VIOLENCE AGAINST WOMEN – IMPACT ON REPRODUCTIVE HEALTH AND PREGNANCY OUTCOME

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Declaration

"I, the undersigned, hereby declare that this the work contained in this thesis is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree."

Signature

Date

ABSTRACT

VIOLENCE AGAINST WOMEN – IMPACT ON REPRODUCTIVE HEALTH AND PREGNANCY OUTCOME

Introduction

Worldwide, up to 25% of women are assaulted during pregnancy, with estimates varying between populations. Violence has been associated with adverse pregnancy outcome, including preterm birth, abruptio placentae and low birth weight. Among the Coloured population of the Western Cape the incidence of spontaneous preterm birth is 20%, compared to the global figure of 10%. Overall, the rate of preterm labour has not dropped over the past 40 years and no clearer answer as to a specific cause has been found.

The objective of this study was to determine whether patients who deliver preterm experience more domestic violence than those who deliver at term.

Methods

Two groups of patients were assessed. Firstly, patients who spontaneously delivered between 24 and 33 weeks (24w0d – 33w6d), who were admitted for suppression of active labour after 24 weeks, or who experienced placental abruption before 34 weeks, were screened for domestic violence using the "Abuse Assessment Screen". A second group of women, attending a local Midwife Obstetric Unit with uncomplicated pregnancies, completed the same questionnaire. The questionnaires were all administered by the same person (J.S.) after written informed consent was given.

Results

A total of 229 patients were interviewed, 99 in the low risk (LR) and 130 in the preterm labour (PTL) group, which included 23 women with abruptio placentae. The PTL group experienced significantly more violence throughout their lives than the LR group (59.7% vs. 40.4%, $p = 0.038$). Experiences of violence within

the last year or during the pregnancy did not reach statistical significance between the two groups, although the numbers were higher for the PTL group. The PTL group smoked significantly more cigarettes per day ($p = 0.009$), used more alcohol ($p < 0.001$) and had a higher incidence of syphilis than the LR group ($p = 0.005$). These differences remained the same when the abruptio's were analyzed as a separate group.

Conclusions: Women who delivered preterm did experience more violence at some point in their lives and were also more likely to engage in high-risk behaviour. Violence alone does not seem to cause PTL directly, but is part of a low socioeconomic lifestyle. The fact that the alcohol use is so high among these women is a problem that needs to be addressed, but once again, it is possibly the result of deeper social problems. The need for education on values and respect, family planning use and low risk sexual behaviour is once again challenged.

OPSOMMING IN AFRIKAANS

GEWELD TEEN VROUE – IMPAK OP REPRODUKTIEWE GESONDHEID EN UITKOMS VAN SWANGERSKAP

Inleiding

Daar word beraam dat tot 25% van alle swanger vroue aangerand word, maar die insidensie wissel tussen verskillende populasies. Ervarings van geweld kan 'n direkte of indirekte oorsaak wees van swak verloskundige uitkoms wat voortydse kraam, abruptio placentae en lae geboortegewig insluit. In die Wes-Kaap, onder die Kleurlingbevolking, is die insidensie van voortydse kraam 20%, wat swak vergelyk met die wêreldwye insidensie van 10%. Gedurende die laaste 40 jaar het die voorkoms van voortydse kraam nie verminder nie en geen deurbrake is gemaak t.o.v die oorsaak van die probleem nie. Die doel van hierdie studie was om te bepaal of vroue wat prematuur verlos moontlik meer geweld ervaar as vroue wat op normale swangerskapsduur verlos.

Metodes

Twee groepe vroue is bestudeer. Die eerste groep het vroue ingesluit wat spontaan verlos het tussen 24 en 33 weke (24w0d – 33w6d) of vroue wat na 24 weke swangerskapsduur toegelaat is vir onderdrukking van kraam. Vroue met plasentale loslating (abruptio placentae) voor 34 weke, sonder onderliggende hipertensiewe toestande, was ook ingesluit in die groep. Daar is m.b.v. 'n vraelys ("Abuse Assessment Screen") bepaal watter van die vroue gesinsgeweld ervaar het. Die tweede groep het vroue ingesluit met ongekompliseerde swangerskappe en wat by 'n nabygeleë kliniek voorgeboortesorg ontvang het. Hulle is ook gevra om die vraelys te voltooi en is opgevolg om die uitkoms van hulle swangerskappe te noteer. Die vraelyste is almal deur een persoon (J.S.) aan die vroue voorgelê nadat hulle ingeligte, skriftelike toestemming gegee het.

Resultate

'n Totaal van 229 vroue was ingesluit, 99 in die lae risiko (LR) groep en 130 in die voortydse kraam (VK) groep, waarvan 23 abruptio placentae gehad het. In vergelyking met die LR groep, het die VK groep het betekenisvol meer geweld in hulle leeftyd ervaar (59.7% teenoor 40.4%, $p = 0.038$). Geweld wat tydens die afgelope jaar of tydens die swangerskap ervaar is, het nie betekenisvol verskil tussen die twee groepe nie, alhoewel die getalle hoër was vir die VK groep. Die VK groep het betekenisvol meer sigarette per dag gerook ($p = 0.009$), meer alkohol gebruik ($p < 0.001$) en het 'n hoër insidensie van sifilis gehad as die LR groep ($p = 0.005$). Hierdie verskille was steeds beduidend nadat dié met abruptio placentae as 'n aparte groep geanaliseer is.

Gevolgtrekking

Die vroue wat prematuur verlos het, het meer emosionele en fisiese geweld in hulle leeftyd ervaar en is meer geneig om 'n ongesonde leefstyl te handhaaf. Geweld blyk nie 'n direkte oorsaak van voortydse kraam te wees nie, maar gaan gepaard met 'n lae sosio-ekonomiese lewensstyl. Die hoë insidensie van alkoholgebruik onder swanger vroue is 'n probleem wat aangespreek moet word, maar dit is waarskynlik die manifestasie van dieper emosionele probleme. Opvoeding in terme van waardes en respek, gesinsbeplanning en veilige seksuele gedrag is gevolglik 'n noodsaaklikheid.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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Thank you to my Father, who was with me all the way.

CHAPTER 1: PARTURITION

1.1 INTRODUCTION

Parturition is the process of giving birth. For such a simple definition, the process is very complicated and is still not fully understood. The process involves a complex interplay of maternal and fetal factors to ensure successful parturition, constituting of five separate physiological events, each having to occur at the appropriate time: membrane rupture, cervical dilatation, myometrial contractility, placental separation and uterine involution.

To be successful, parturition requires that those fetal organs, necessary for survival outside the uterus, have matured and that the mother has undergone the necessary changes for lactation. Synchronous maturation of the fetus and stimuli to increase uterine activity is therefore desirable and evidence suggests that it is the fetus itself that triggers both these series of events.[1]

During the first 95% of the duration of normal pregnancy the myometrial smooth muscle is relatively unresponsive to natural stimuli and the myometrial activity is characterised by poorly co-ordinated contractures, commonly known as Braxton-Hicks contractions.[2] These contractions are of short duration, low-amplitude and isolated to regionalised areas of the myometrium.[1,3] At the time of labour, the uterus develops high-frequency, high-amplitude contractions and the myometrium is now excitable, spontaneously active and responsive to uterotonins, uterine smooth muscle contractants, such as oxytocin and prostaglandins.[3] The transition from the quiescent state to the excitable state is termed "activation" and once this has occurred the uterus can undergo "stimulation" in response to stimuli that may be local, maternal, mechanical or fetal.[2]

During pregnancy, uterine activity can be divided in three distinct phases:[2]

1. Phase 0 – during this phase the uterus is relatively quiescent and is like that for most of the pregnancy.
2. Phase 1 – occurs in late gestation with the activation of the myometrium and corresponds clinically with the first stage of labour, i.e. the time from the first contraction until full dilatation of the cervix. The initiation of parturition thus correlates most closely with the transition from phase 0 to phase 1.
3. Phase 2 – here the activated myometrium responds to various uterotonins and brings about the delivery of the fetus, synonymous with the second stage of labour.

The delivery of the placenta, the third stage of labour, and the puerperium (maternal recovery from childbirth, lactation and the restoration of her fertility) are sometimes referred to as "phase 3" of labour.[4] Placental separation generally occurs by cleavage along the plane of the decidua basalis and uterine contraction is essential to prevent haemorrhage from the exposed sinuses after delivery of the placenta.[5] Phase 3 is associated with the release of maternal oxytocin and uterine atony is generally managed with the administration of intravenous oxytocin or prostaglandin $F_{2\alpha}$.[5]

1.1.1 Myometrial contractions

There are unique characteristics of myometrial smooth muscle cells compared with skeletal muscle.[4] The degree of shortening with contractions may be one order of magnitude greater than that attained in striated muscle cells.[3] Forces in smooth muscle cells can be exerted in any direction, whereas the contraction force generated by skeletal muscle is always aligned with the axis of the muscle fibres.[4] In the myometrium, the thick and thin filaments are found in long, random bundles throughout the cells. This arrangement facilitates greater

shortening and force-generating capacity of smooth muscle. The advantage of multidirectional force generation in myometrial smooth muscle is that it allows variability in the directionality of the expulsive force that can be brought to bear, irrespective of the presentation of the fetus.[4]

Myometrial contractions are dependent on conformational changes in the actin and myosin molecules, allowing the filaments to slide over each other (crossbridge "cycling" of the myosin head) and thus leading to the shortening of the myocyte.[6] This interaction is essential for the muscle to contract. These changes require adenosine triphosphate (ATP), which is generated by myosin after phosphorylation of the 20 kDa light chains of myosin by the enzyme myosin light chain kinase (MLCK).[1] This process is activated by calcium ions through interaction with calmodulin, a calcium-binding protein, which, in turn requires 4 calcium-ions for it's own activation.[1] Myosin light chain kinase can also undergo phosphorilation by protein kinase A (PKA), a cyclic AMP-activated protein kinase, which reduces the affinity for calcium-calmodulin and leads to its inactivation.[6]

1.1.2 Differentiation of uterine activity

During active labour, the uterus is transformed into two distinct parts: the upper segment, or fundus, and the lower segment, which includes the cervix.[4] The actively contracting fundus becomes thicker as labour advances; the myometrium of the upper segment does not relax to its original length after contractions, but becomes relatively fixed at a shorter length. The tension, however, remains the same as before the contraction.[4] In comparison, the lower segment and cervix is relatively passive and it develops into a much more expanded thinly walled passage for the baby. Relaxation of the lower segment is not a complete relaxation, but rather the opposite of retraction – the fibres that stretch with each contraction, do not return to its previous length and remains relatively fixed at the shorter length.[4] The lower segment develops gradually

during gestation and thins remarkably during labour. If the entire uterine wall was to contract simultaneously and with equal intensity, the net expulsive force would be markedly decreased, indicating the importance of the division of the uterus into two distinct segments, differing not only anatomically, but also physiologically.[4]

1.1.3 The cervix

During gestation, a firm and closed cervix is essential for an uneventful pregnancy, allowing adequate time for the maturation of the fetus.[7] Before the onset of labour, during the phase of uterine activation (phase 1), the cervix is softened, thus facilitating dilatation once forceful myometrial contractions begin.[4] The effective force of the first stage of labour, the uterine contractions, exerts hydrostatic pressure through the fetal membranes or presenting part against the cervix and lower segment. As a result, effacement and dilatation take place in the already softened cervix. Effacement takes place from above downward and literally means that the cervical fibres at about the level of the internal os are "taken up" into the lower uterine segment, while the external os remains temporarily unchanged.[4]

The cervix and lower segment are regions of lesser resistance and during contractions are subjected to distention, in the course of which centrifugal pull is exerted on the cervix. As the uterine contractions cause pressure on the membranes, the hydrostatic action of the amniotic sac in turn dilates the cervix and in the case of already ruptured membranes, the pressure of the presenting part of the fetus is similarly effective.[4] This metamorphosis of the cervix from an organ closing the uterus to a passage of more than 10cm in diameter for delivery of the baby is the result of active and dynamic reorganisation processes within the extracellular matrix.[7] Unfortunately, due to ethical and methodological reasons, it has not yet been possible to fit the individual biochemical components

of ripening and dilatation together. As caesarean hysterectomies are very rare, the entire cervix is hardly ever available for biochemical analysis and biopsy samples of cervical tissue cannot be obtained in all stages of pregnancy. When samples are available, they were not always from the same region in the uterus or taken at the same time during pregnancy. [7]

1.2 PHASE 0 OF PARTURITION: INHIBITION OF MYOMETRIAL ACTIVITY

Agents that inhibit myometrial activity do so by increasing the intracellular levels of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP). These cyclic nucleotides inhibit the release of calcium ions ($Ca^{2+)}$ from intracellular stores or reduce MLCK activity.[2]

Relaxin, when binding to myometrial receptors, activates adenylate cyclase activity and thus an increase in cAMP generation. It also inhibits oxytocin-induced turnover of phosphoinositide through cAMP-dependant protein kinase. Relaxin is expressed in the fetal membranes, placenta and decidua[8] and has been found at higher concentrations at these sites in patients with premature rupture of the membranes. Another function of relaxin is that it also increases levels of the matrix metalloproteinase enzymes, which are normally involved in remodeling cervical connective tissue at term. [5]

Receptors for prostacyclins, which represent the major eicosanoid present in the myometrium, have also been identified in the human.[9] There are significant concentrations of at least two forms of prostaglandin E_2 receptors found in the myometrium and one of them, the EP_2 receptor, causes relaxation through cAMP formation.[9]

Nitric oxide (NO) is synthesised from L-arginine by one or more isoforms of NO synthase in the amnion, chorion, decidua and myometrium.[5] Nitric oxide acts to

relax the myometrium through cGMP, altering levels of intracellular Ca^{2+}. It has been suggested that NO functions in a paracrine manner, in conjunction with progesterone, to suppress myometrial contractility.

Progesterone inhibits spontaneous uterine contractility as well as stimulated activity throughout pregnancy. The placenta is the major source of progesterone after 6 weeks of gestation. In the syncytiotrophoblast the enzyme 3β-hydroxysteroid dehydrogenase type 2 (3β-HSD-2) is expressed and it converts pregnenolone to progesterone. Pregnenolone is derived from low-density lipoprotein (LDL) from maternal circulation taken up from the intravillous pool of blood by the receptors of the syncytiotrophoblast layer. The chorion also produces progesterone from pregnenolone in the trophoblast cells[10] (see below).

1.3 PHASE 1 OF PARTURITION: ACTIVATION OF THE MYOMETRIUM

The switch from myometrial quiescence to activation is essential in order for the muscles to respond to the stimulation provided by the high levels of uterotonic agents, the end-point being the synchronous, high-amplitude, high-frequency contractions associated with active labour.

The onset of labour requires both endocrine and mechanical signals generated by the fetal genome.[1] Fetal growth increases the uterine stretch and thus the myometrial tension, while activation of the fetal hypothalamic-pituitary adrenal (HPA) axis literally "switches" on placental endocrine function.[1] The overall regulation of myometrial activity, however, is genetically regulated and several animal studies have suggested that it is the genotype of the fetus that controls the length of the pregnancy.[11]

Phase 1 is manifested through the increased expression of a group of proteins, collectively termed contraction-associated proteins or CAP's. Included in this cassette are:[5]

- Ion channels – determine the resting membrane potential and hence the excitability of myocytes
- Agonist receptors – including oxytocin and prostaglandin receptors, enabling the myometrium to respond to these stimulants
- GAP junctions – connexin-43 (Cx-43) is the major protein of myometrial gap junctions, essential for cell-to-cell coupling.

1.3.1 The fetal hypothalamus-pituitary adrenal axis

Animal studies, mostly performed on sheep and goats, concluded that in those species the fetus, *in utero*, provided the trigger for the onset of labour and that it was through the activation of the fetal HPA-axis, with the endpoint being progesterone withdrawal.[2] In human pregnancies, however, the maternal circulation levels of progesterone remain high and only decline after the delivery of the placenta.[2,4,5] The argument resulting from these findings is that primate parturition is regulated differently from animals, but with the fetal HPA-axis still involved in the process.[2] Activation of the HPA-axis of the primate fetus occurs in late gestation, as in other animal models.

The fetal adrenal can be divided into three distinct zones:[5]

- An outer adult (definite) zone produces predominantly aldosterone in late gestation.
- An inner fetal zone, producing dehydroepiandrosterone sulphate (DHEAS) from early gestation (20 weeks). The fetal zone is functional during pregnancy only, dramatically increasing in size and steroidogenic activity as gestation advances. After birth, rapid involution occurs[3] and it has no counterpart postnatally.[12]

- A transitional zone between the adult and fetal cortex, which produces cortisol.

Cortisol produced by the fetal adrenals plays a major role in fetal development, by promoting maturation of the lungs, liver, thyroid and gut, essential for extrauterine life.[12] In some species, fetal adrenal cortisol provides the trigger for the onset of labour, but this is not the case in primates.[3] The principal steroid product of the primate fetal adrenal is the androgenic 19-carbon steroid, DHEAS.[3,13]

During the second half of pregnancy, adrenocorticotropic hormone (ACTH) stimulates steroidogenesis in the transitional and fetal zone[5] and is essential for the growth of the fetal zone.[14] Fetal ACTH output is relatively suppressed during pregnancy by the negative feedback of cortisol derived from the maternal circulation via the placenta. Maternal cortisol is converted to biologically inactive cortisone in the placenta through the working of the enzyme 11ß-hydroxysteroid dehydrogenase (11ß-HSD-2), which is stimulated by placental estrogens, and in late pregnancy there is an increase in activity due to the rise in estrogen levels.[10] There is, therefore, less maternal cortisol entering the fetal compartment, less negative feedback and a subsequent rise in fetal ACTH concentrations and cortisol synthesis, actions which correlates with the activation of the fetal HPA axis. However, excessive exposure to endogenous or exogenous corticotropin-releasing hormone (CRH) inhibits the function of 11ß-HSD-2, resulting in higher levels of maternal cortisol entering the fetal circulation, which may, in turn, lead to early activation of the fetal HPA-axis.[15]

Adrenocorticotropic hormone is the major tropic factor for the fetal adrenal gland; it increases the expression of its own receptor in the fetal adrenal cortical cells and results in the up-regulating of key enzymes in the steroidogenic pathway.[5] Activation of fetal HPA function is also associated with increased levels of CRH mRNA in the parvocellular neurons of the paraventricular nucleus of the fetal

hypothalamus and of pro-opiomelanocortin (POMC), the precursor to ACTH.[5] It has been suggested that, in addition to ACTH, the fetal zone is also regulated by a pregnancy-specific factor,[3] as postnatal involution still occurs despite ongoing exposure to ACTH. This factor may be CRH, as the relative size of the fetal adrenal zone follows the pattern of CRH secretion in the placenta and in humans, both peak near the time of parturition.[16] Furthermore, CRH declines dramatically in both the maternal and fetal circulation's postpartum, coinciding with the involution of the fetal zone.[3] Smith *et al.* recently found the steroidogenic effects of CRH on human fetal adrenal cortical cells to be preferential for DHEAS-production with no significant effect on cell mitogenic activity.[3] The effect of CRH on the fetal adrenal is mediated through CRH-receptors on fetal zone cells and this receptor is similar to the type-1 receptor identified in the pituitary. Activation of the CRH-receptor leads to increased expression of the enzymes required for DHEAS-synthesis, i.e. P450scc and P450c17.[3]

Activation of the fetal HPA axis can also take place in response to an adverse intra-uterine environment, e.g. hypoxaemia or intra-uterine infection. Short-term hypoxaemia results in increases in plasma ACTH and cortisol constricts fetal circulation, which correlates with increased levels of CRH mRNA and POMC mRNA in the fetal hypothalamus and pituitary, respectively.[2] After prolonged hypoxaemia there are additional increases in pituitary POMC mRNA levels, reflecting upregulation of key enzymes for cortisol biosynthesis in the fetal adrenal gland.

It is becoming increasingly clear that the primate fetus does play a role in the initiation of parturition.[5] During late gestation, there are increased levels of POMC mRNA in the fetal pituitary, and it is likely that this is provoked by increased output or action from hypothalamic CRH.[5]

Estrogen is important for the normal process of parturition. It has been established that humans, like sheep, have a feto-placental unit of estrogen production by which C-19 androgen precursors form the fetal adrenal gland can be secreted and aromatised in the placenta to form estrogen.[2]

1.3.2 Estrogen production during pregnancy

As there is a virtual absense of placental 17α-hydroxylase/17-20 desmolase (P450c17) activity in the human placenta, progesterone and prenenolone cannot be converted to androstenedione and dehydroepiandrosterone (DHEA) for estrogen production.[10]

In early gestation, the androgen precursors are derived from the maternal circulation, but by week 20 the vast majority of estrogen is derived from fetal androgens.[10] The major androgenic precursor, DHEAS, derived mainly from the fetal adrenal, is aromatised by the placental aromatase (P450arom) enzyme system.[13] The placenta has an abundance of this sulfatase enzyme and DHEA is converted to DHEAS in the placenta, then to androstenedione, testosterone and finally to estrone and 17ß-estradiol.[13] Estriol, with a 16α-hydroxyl group, is the estrogen produced in the largest quantities during pregnancy and, as the placenta lacks 16α-hydroxylation ability, must be derived from an immediate fetal precursor. The fetal adrenal, with 16α-hydroxylation activity in the liver, provides the 16α-hydroxydehydroepiandrosterone sulfate (16α-OH-DHEAS) for placental estriol production (Figure 1.1).[10] Estriol formation demonstrates the interdependence between the fetus, placenta and mother; the so-called "fetoplacental-maternal-unit".[13]

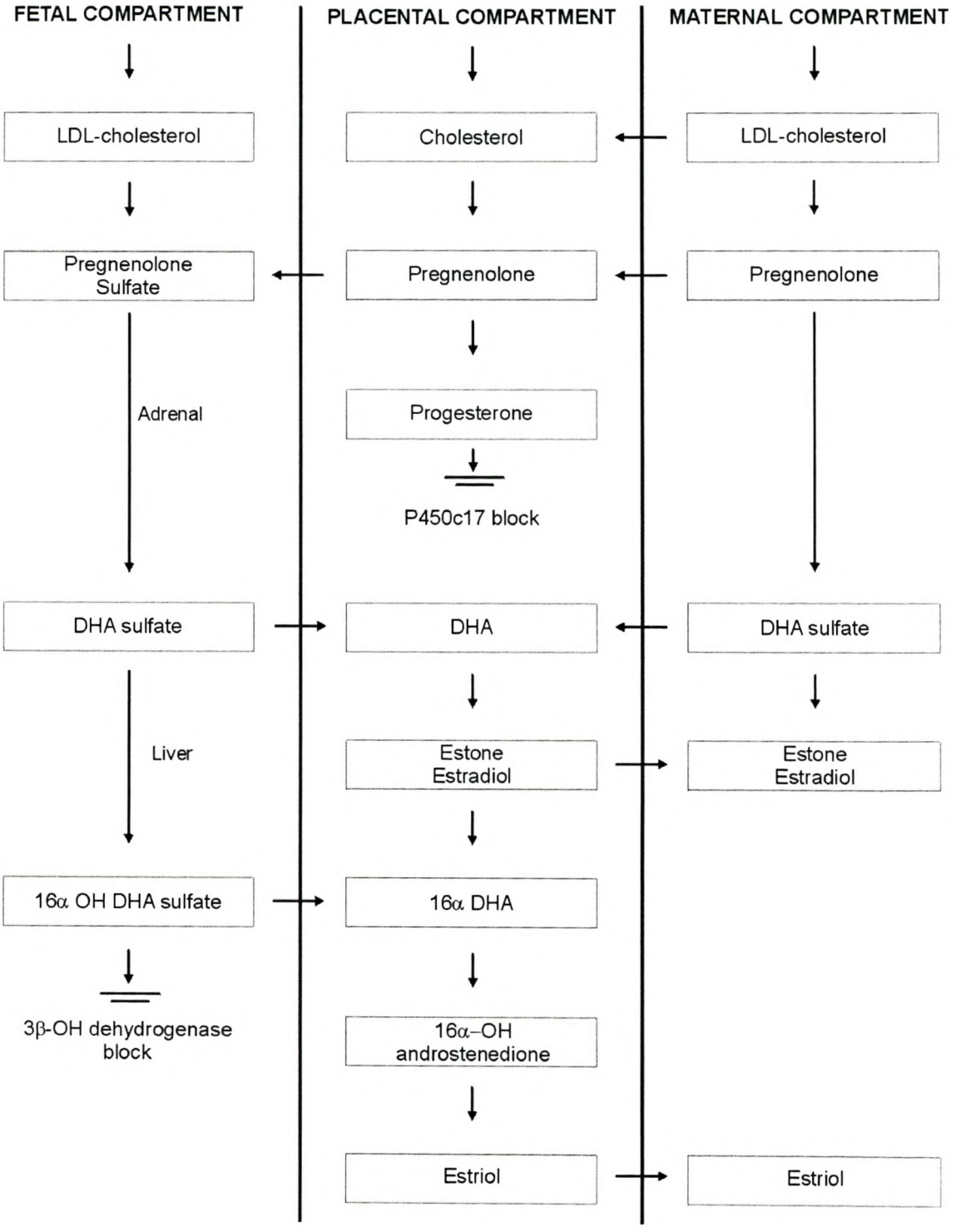

Figure 1.1 The interaction between the maternal, placental and fetal components in estrogen production during normal pregnancy. Adapted from Speroff *et al.* [10]

1.3.3 Progesterone and human pregnancy

Progesterone is largely produced by the corpus luteum until about the 10th week of pregnancy with the luteoplacental shift occurring at around week six to seven.[10] Low-density lipoprotein (LDL) cholesterol and pregnenolone, the precursors to progesterone, are obtained from the maternal bloodstream for progesterone synthesis. Progesterone is synthesised by placental syncytiotrophoblasts and chorionic trophoblasts[2] and most of the progesterone produced in the placenta enters the maternal circulation (Figure 1.2).[10]

There is evidence in the baboon that estradiol regulates progesterone production in the placenta. The fetoplacental units in human and baboon pregnancies are virtually identical.[17] In the human syncytiotrophoblast, estradiol increases progesterone production by increasing LDL-cholesterol uptake. Estrogen also increases the placental cytochrome P450 cholesterol side chain cleavage (P450scc) enzyme activity that converts cholesterol to pregnenolone.[10]

Progesterone also serves as a substrate for the fetal adrenal gland to produce glucocorticoids and mineralocorticoids. The fetal zone in the adrenal gland lacks the 3β hydroxy-steroid dehydrogenase/Δ^{4-5} isomerase (3β-HSD) and must therefore utelize placental progesterone for cortisol synthesis.[10]

High concentrations of progesterone are required during pregnancy for the maintenance of uterine quiescence. In lower species and non-primate mammals, a fall in plasma progesterone concentration is the single most common endocrine event associated with parturition.[2,10,18] In humans the role of progesterone is less clear, largely because of the inability to demonstrate any fall in plasma or tissue progesterone levels prior to the onset of labour in women.[1,10]

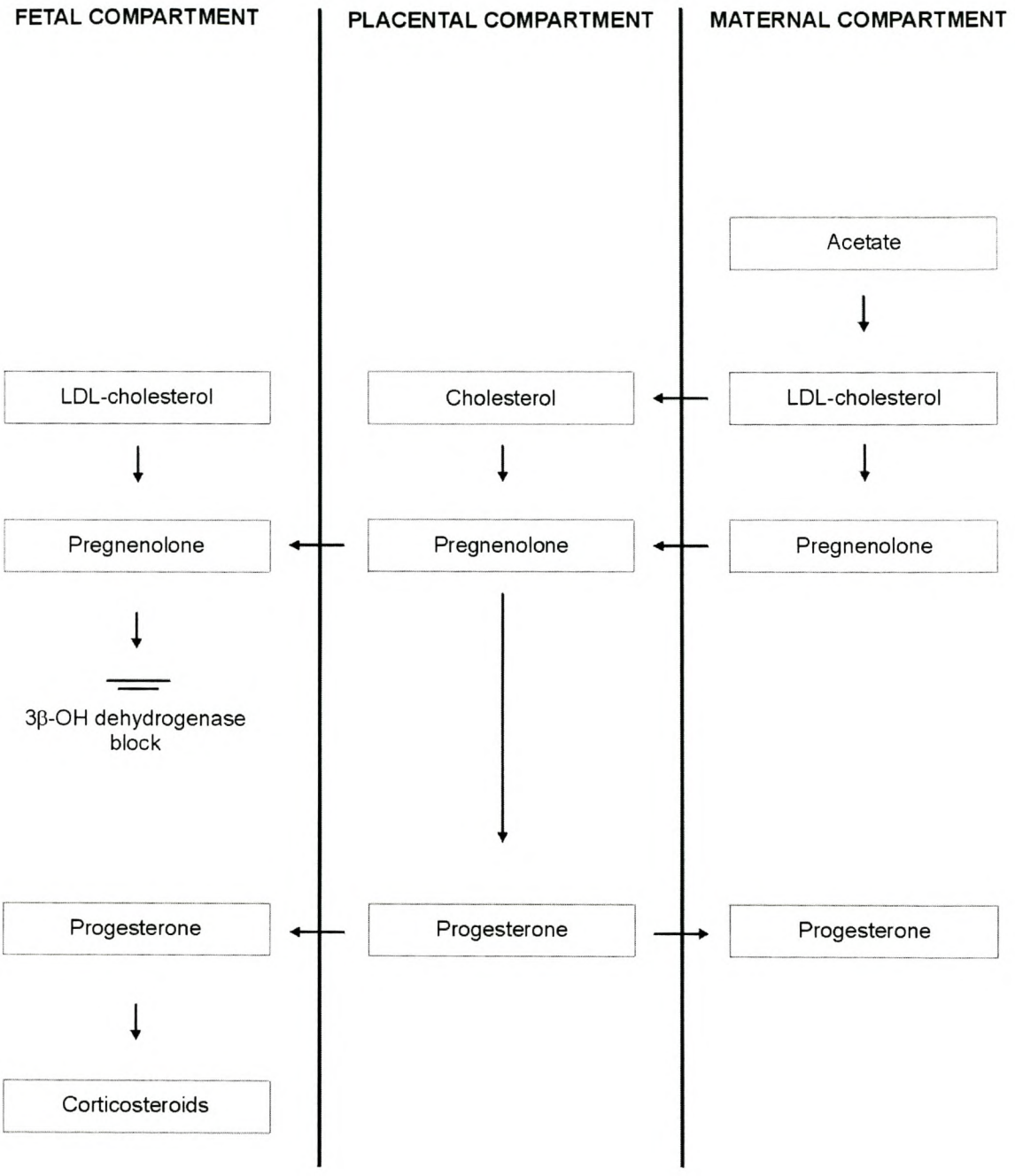

Figure 1.2 The interaction between the maternal, placental and fetal components in progesterone production during normal pregnancy. Adapted from Speroff *et al.* [10]

In most species, administration of exogenous progesterone at term blocks the expression of the CAP genes and inhibits the onset of labour.[1] Moreover, the progesterone antagonist, mifepristone (RU486), administered late in human pregnancy, activates many of the pathways involved in the onset of labour.[19] This provides evidence that progesterone is necessary for the maintenance of pregnancy[1] and suggests that a decline in progesterone activity, without an actual fall in concentration, could be an important component of the initiation of parturition in women.[18]

There have been speculations that a progesterone metabolite, interacting with the progesterone receptor, could act as a progestogen in the human and that the levels of this steroid fall prior to labour.[1] Another alternative is that a progesterone antagonist may induce progesterone withdrawal at term, but to date there has been no clear data to support either of these possibilities.[1] Erb *et al.* have searched for progesterone metabolite whose levels decrease prior to labour but none has thus far been identified.[1]

Erb and Lye (unpublished data) also tested the hypothesis that changes at the levels of the progesterone receptor or expression of receptor activators might induce functional withdrawal of progesterone in the myometrium, but have to date not been successful.[1] The possibility that the progesterone receptor system remains functional during all of pregnancy can therefore not be excluded.

Karalis and co-workers found that glucocorticoid receptors, but not progesterone receptors, are present in trophoblast cells in late pregnancy and that progesterone, binding to these glucocorticoid receptors, inhibits CRH expression.[18] They also suggested that at term, the exponential rise in CRH and cortisol displace progesterone from these binding sites and this could explain why the plasma concentrations of progesterone remain high at term and during labour in humans.

Other studies of gene expression in the human myometrium have focussed on the lower uterine segment and have led to the suggestion that the progesterone receptor system is functional in this region during labour.[2,20,21]

Teoh and co-workers compared the expression of CAP genes in samples of myometrial tissue from the lower uterine segment from women who underwent elective caesarean section (not in labour) with samples from women in active labour who subsequently were delivered surgically for fetal distress.[1] They observed an increase in the expression of the three genes that are expected to be associated with myometrial relaxation: connexin-26, EP-4 receptor and the CRH-1 receptor (CRH-R1). The latter two are linked to the generation of cAMP, which relaxes the myometrium, and it is known that connexin-26 is positively regulated by progesterone.[2] They did not, however, observe an increase in the expression of CAP genes, including CX-43, oxytocin receptors or prostaglandin receptors that are all linked to stimulatory pathways in the myometrium.[20,21] Recently, Stevens *et al*. reported that CRH-R1 was expressed at elevated levels in the myometrium and fetal membranes collected from patients at term and preterm labour.[20] Importantly, the levels of CRH-R1 were consistently much higher in the lower uterine segment than in the fundal tissue.

Sparey *et al*. found levels of prostaglandin H_2 synthase type 1 and type 2 (PGHS-1 and PGHS-2) to be expressed at greater levels in the lower, than in the upper uterine segment.[21] At the same time, connexin-43 protein was expressed at much higher levels in the fundus and was even more pronounced at parturition.[21] Both PGHS-1 and PGHS-2 synthesise prostacyclin (PGI_2), PGE_2 and $PGF_{2\alpha}$, which are all involved in regulating myometrial activity during gestation and labour.[22] The higher concentrations of these enzymes in the lower uterine segment may increase PGI_2 and PGE_2 production, which, in turn,

increases the collagenolytic activity of the cervix.[21] Prior to labour this results in cervical ripening and once labour has begun the increased local production of these prostaglandins may then facilitate cervical dilatation.[22]

How can this data be reconciled with myometrial activation and the generation of the contractions of labour?

Challis *et al.*[2] and Lye and co-workers[1] speculate that during pregnancy, progesterone inhibits the expression of CAP genes within the myometrium, maintaining the muscle in a quiescent state. At the time of labour the myometrium exhibits a regionalisation of function, which is engineered by progesterone. The myometrium in the lower segment expresses genes that contribute to relaxation, while expression of CAP genes in the fundus is increased and thus fascilitating descent of the fetus to ensure efficient delivery.[1,2]

An early study supports this hypothesis. The *in vitro* response of myometrial strips from the fundus and lower uterine segment to PGE_2 and $PGF_{2\alpha}$ was examined. Before labour, $PGF_{2\alpha}$ had little effect on the fundal myometrium, but stimulated the strips from the lower segment.[23] Both the prostaglandins stimulated fundal myometrium during active labour and while $PGF_{2\alpha}$ had no effect on lower segment myometrium during that time, PGE_2 induced inhibition of contractility.[23]

The change in expression of CAP genes in samples of fundal myometrium during labour needs to be determined in order to prove the concept of molecular and function regionalisation of the myometrium.[1]

The data suggesting that the progesterone receptor system is functional in the lower uterine segment during labour, raise the possibility that elevated levels of

progesterone may actually be necessary to support the establishment of an inhibitory lower segment.[1] This would require mechanisms within the fundus that would block the inhibitory actions of progesterone and allow the expression of CAP genes for generation of contractions during labour.

1.3.4 The effect of physical uterine distention

It has been established that CAP gene expression is dependent on endocrine signals, but recent data suggest that these signals are not sufficient in themselves to account for the increases in CAP expression seen during labour.[1]

Ou and Lye, studying unilaterally pregnant rats, found that while CAP gene-expression, CX-43 and oxytocin receptors increased in the pregnant horn during labour, there was not a parallel increase in the non-gravid horn, even though both horns were exposed to the same hormonal changes.[11]

In a series of subsequent experiments they explored the possibility that uterine stretch may be a critical component of the mechanism that regulates CAP expression during labour.[1]

Their data suggests that the stretching of the uterus contributes to the up-regulation of CAP's, but is dependant on the endocrine environment. The molecular mechanism behind this phenomenon remains to be determined (Figure 1.3).

The contribution of stretch to myometrial activation may be the underlying cause of the increased incidence of PTL in multiple pregnancies. In theory, myometrial tension must be increased in these pregnancies, since, in comparison with singleton pregnancies, there is no increase in amniotic pressure even though uterine diameter is increased.[1]

If uterine wall tension contributes to the regulation of CAP gene expression in the myometrium, the processes which control the growth of the uterus during pregnancy will be important, because of the impact that growth has on development of tension.

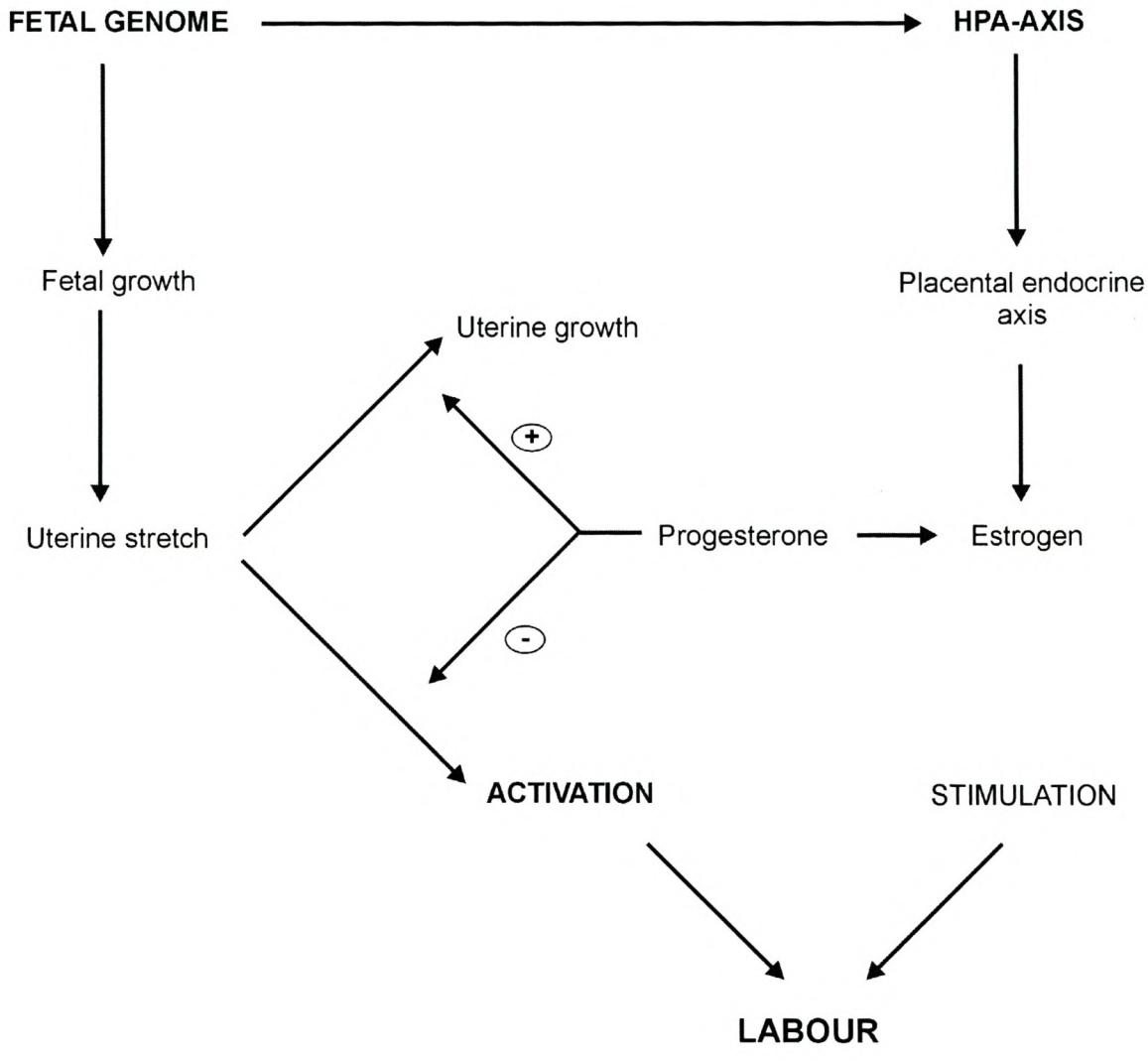

Figure 1.3 Input of mechanical distention of the uterus in the initiation of labour. Adapted from Lockwood *et al.* [79]

Lye and colleagues propose that uterine growth occur in three stages during pregnancy.[1] During the first trimester, uterine growth is largely due to hyperplasia which is controlled by endocrine factors, such as estrogen and progesterone. In the second and early third trimesters, uterine growth is closely matched to, and possibly controlled by, fetal growth. Finally, by the late third trimester there is a decline in uterine growth compared with fetal growth, leading to a marked increase in uterine wall tension or physical stretch.[1]

They speculate that progesterone is necessary to support stretch-induced hypertrophy of the uterine wall. In most species, the fall in progresterone at term no longer stimulates uterine growth, leading to a marked increase in wall tension due to continued fetal growth, which in turn, results in increased CAP gene expression and contributes to myometrial activation.[1]

1.4 PHASE 2 OF PARTURITION: MYOMETRIAL STIMULATION

After the myometrium has undergone the activation phase, it is prepared for optimal response to those myometrial stimulants that drive the muscle to contract during labour. Of the many agonists that stimulate myometrial contractions, the most convincing information is available for oxytocin and stimulatory prostaglandins.[1,2]

1.4.1 The role of oxytocin

Oxytocin is a nonapeptide and is synthesised by hypothalamic magnocellular neurons located in the supraoptic and paraventricular nuclei.[2,24] Hypothalamic oxytocin is released into the circulation from the posterior pituitary promoting myometrial contractility during late pregnancy and parturition and stimulating milk release from the mammary glands in lactation.[25] Oxytocin is one of the most potent uterotonic agents and is used clinically in obstetric practice to induce or augment labour.[24]

Prior to parturition there is an increase in maternal plasma levels of oxytocin, occurring first only at night,[28] but once labour has begun, oxytocin levels rise significantly, especially during the second stage.[10] The proposal is therefore that the major role of oxytocin is developing the more intense contractions, necessary for the passing of the fetus through the birth canal.[1,10]

Oxytocin is also synthesised locally in the amnion, chorion and decidua,[27] which may be a significant stimulus for myometrial and membrane production of prostaglandins.[28]

Cervical dilatation also appears to be dependent on oxytocin stimulation of prostaglandins, probably in the decidua.[10]

In addition to oxytocin levels in the maternal circulation, the action thereof may also depend on the myometrial sensitivity to oxytocin. The levels of oxytocin receptors in the myometrium are low in the nonpregnant state, increasing steadily up to 80-fold throughout gestation and doubling during parturition.[10] This receptor concentration correlates with the uterine sensitivity to oxytocin,[29] but the mechanism of the increase is largely unknown.[10]

1.4.2 The role of prostaglandins

There is compelling evidence that supports a role for prostaglandins in human parturition, term and preterm.[2,30] Prostaglandins contribute to the transition from phase 1 to phase 2, rather than initiating the labour process.[2]

Prostaglandin $F_{2\alpha}$, thromboxane A_2 and sometimes PGE_2 are potent stimulators of uterine contractility in most species.[1] Whether stimulatory prostaglandins are

initiators of labour is debatable, but there is no doubt that these uterotonic agents do play an important role in the generation of labour contractions.[1] Increased levels of prostaglandins in maternal plasma and amniotic fluid during labour, suppression of term and preterm labour though inhibition of prostaglandin synthesis and induction of labour by administration of prostaglandins clearly demonstrate the role of prostaglandins in parturition.[10,31]

Prostaglandins, including PGE_2 and $PGF_{2\alpha}$, are formed from the obligate precursor, arachidonic acid, which is liberated from membrane phospholipids through the activities of one or more isoforms of phospholipase C (PLC) or phospholipase A_2 (PLA_2).[5] The activity of these enzymes increases with increasing length of gestation.[10] Arachidonic acid is converted to PGH_2 through the cyclo-oxygenase (COX) enzyme, prostaglandin H2 synthase (PGHS) and then through a series of isomerases, to primary prostaglandins by specific prostaglandin synthases.[5,10,32] There are two forms of PGHS enzymes which are 70 - 72 kDa heme proteins, but products of different genes.[5] Prostaglandin H_2 synthase-1 (PGHS-1 or COX-1), which is described as constitutive, is found in virtually all tissues and produces prostacyclin, a potent vasodilator.[10] Prostaglandin H_2 synthase-2 (PGHS-2 or COX-2), the inducible form, is expressed only after stimulation by various growth factors, cytokines, endotoxins and also glucocorticoids in the human amnion.[5,10,33]

The primary prostaglandins are metabolised through a NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase (PGDH) enzyme that catalyses 15-oxydation to form inactive metabolites.[5] Prostaglandin dehydrogenase expression and activity is especially high in human chorionic trophoblast cells during pregnancy and it has been suggested that this may provide a metabolic barrier, preventing passage of active prostaglandins from the amnion and chorion from reaching the underlying decidua and myometrial tissue.[5] In support of this

hypothesis, Sangha *et al.* reported decreased expression and activity of PGDH in the chorio-decidual tissue during term and preterm labour.[34]

Prostaglandin action is effected through specific G-protein coupled receptors.[5] These include four main subtypes for PGE_2, namely EP-1, EP-2, EP-3 and EP-4, and the FP-receptors for $PGF_{2\alpha}$. The EP-1 and EP-3 receptors mediate contractions of smooth muscle through increased calcium mobilisation by activating PLC and inhibition of intracellular cAMP by inhibiting adenylate cyclase.[4,5] Activation of EP-2 and EP-4 receptors increase cAMP formation and relaxes smooth muscle. The different receptor subtypes are expressed in human myometrium throughout gestation,[5] explaining why PGE_2 may have different effects in different areas of the uterus. For example, at low concentrations, PGE_2 stimulates $G\alpha s$-induced adenylate cyclase expression, causing myometrial relaxation, while at higher concentrations, PGE_2 may inhibit adenylate cyclase (through $G\alpha i$) or activate phospholipase C (through $G\alpha q$), causing increased myometrial contractions.[4]

In human pregnancy, prostaglandin synthesising and metabolising enzymes are discretely compartmentalised within the layers of fetal membranes.[32] The human amnion contains little PGDH activity, PGHS-2 activity predominates and it is the major site of PGE_2 synthesis.[32] At term and preterm labour, mRNA levels and activity of PGDH-2 increase significantly.[35] The chorion expresses both PGHS and PGDH activity, with PGDH dominating during gestation.[2] During term labour PGHS-2 activity increases while PGDH declines.[5] During preterm labour, activities of both PGHS subtypes increase in the chorion.[5] Human decidua also produces both types of PGHS enzymes, but there is little change in PGHS mRNA levels in these tissues at the time of labour.[5] Studies on prostaglandin production from myometrium collected from women at the time of labour have led

to conflicting findings.[36] While some investigators reported increased prostaglandin output, most have failed to demonstrate increasing prostaglandin synthesis or PGHS activity in myometrium collected from women in term or preterm labour. It therefore still remains unclear whether those prostaglandins that stimulate myometrial contractility are generated in myometrium decidua or in the amnion-chorion layers.[5]

Regulation of prostaglandin production from human fetal membranes is multifactorial[37] and not necessarily the same during term and preterm labour.[2] Output of PGE_2 and increased levels of PGHS mRNA in amnion and chorion are stimulated by glucocorticoids. Increased expression of PGHS-2 also occurs in response to a variety of growth factors, including epidermal growth factor (EGF), and cytokines such as interleukin-1 (IL-1), tumour necrosis factor (TNF) and interleukin - 6 (IL-6).[37]

1.4.3 Prostaglandin metabolism

The biologically active levels of prostaglandins depend not only on rates of it's synthesis, but also on the rates of metabolism.[32] The absence of PGDH in chorion trophoblasts may therefore predispose to premature delivery as it normally prevents prostaglandins from reaching the decidua and myometrium.[5] Approximately 10 to 15% of patients in idiopathic preterm labour have diminished levels of PGDH but normal presence of trophoblasts, and many patients presenting in preterm labour with underlying infection have virtually no PGDH, which is associated with loss of chorionic trophoblast cells (Figure 1.4).[2,21]

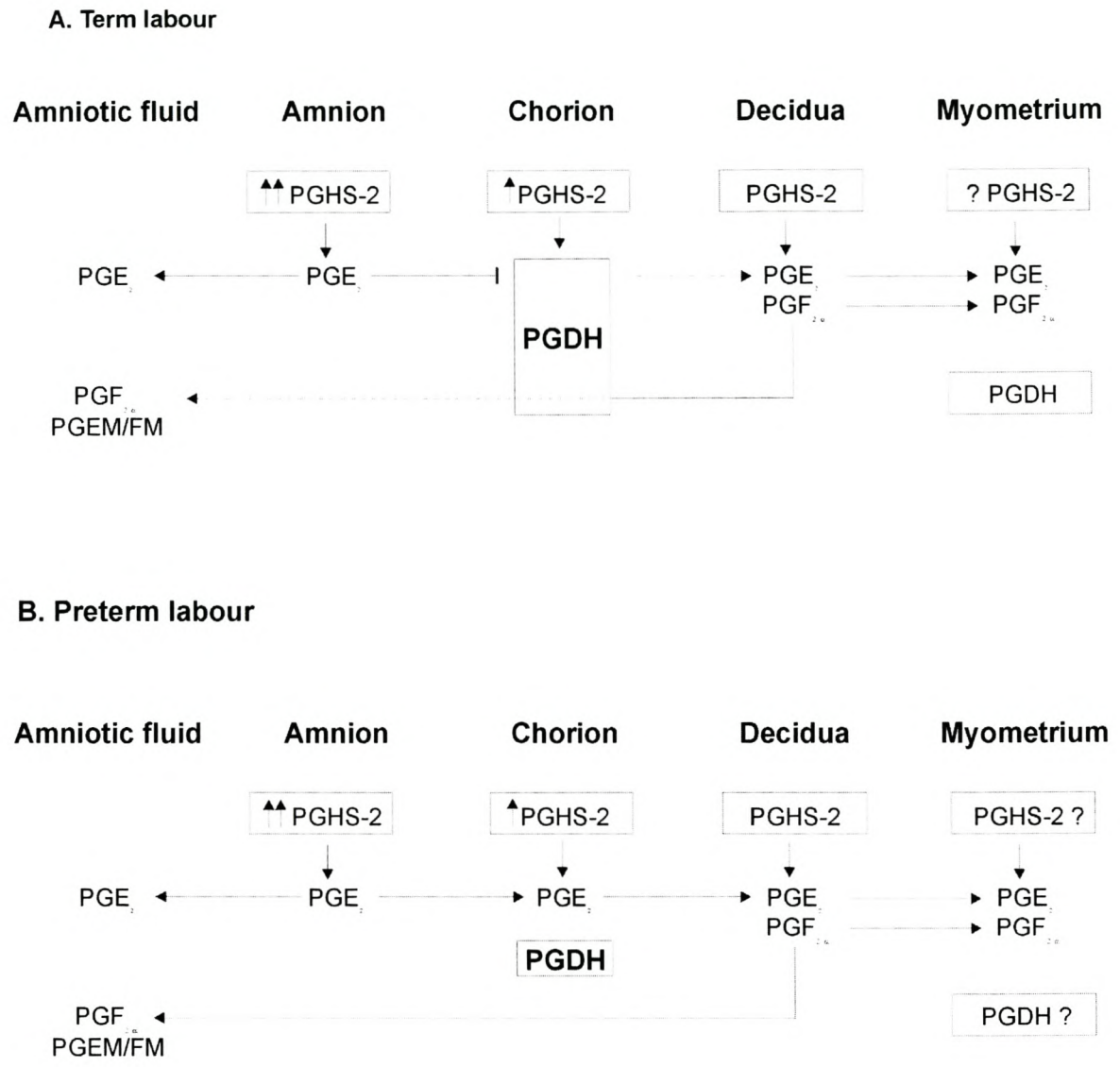

Figure 1.4 Diagrammatic presentation of the sites of prostaglandin synthesis and metabolism at term and preterm labour. Adapted from Challis *et al.*[2]

PGDHS-2 = prostaglandin H synthase 2

PGDH = 15-OH prostaglandin dehydrogenase

Recent studies suggest that progesterone sustains PGDH activity while glucocorticoids and cytokines down-regulate PGDH mRNA levels, synthesis and enzyme activity.[38] Patel *et al.* have demonstrated that chorionic PGDH expression and activity is inhibited by cortisol, betamethasone and dexamethasone and that it is maintained by progesterone.[38] Chorion trophoblasts express the enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD), which converts pregnenolone to progesterone.[36] The ability of progesterone to maintain PGDH activity can be reversed with trilostane, an inhibitor of 3β-HSD, or by RU486, a progesterone receptor antagonist.[5] This observation suggests that progesterone, produced locally in the chorion, maintain PGDH activity through interaction with glucocorticoid receptors.[36] At term there is an increased availability of endogenous cortisol, which displaces progesterone from glucocorticoid receptors, resulting in the inhibition of PGDH activity.[36]

An interesting finding by Challis and co-workers is that biologically inactive cortisone was almost as effective as cortisol in inhibiting PGDH in chorion cells, but not in placental trophoblast cells.[32] In the chorion, cortisone is converted to active cortisol by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1).[5]

It seems that there is also a regional distribution of PGDH activity in human fetal membranes.[32] Van Meir *et al.* found that chorion, collected from the region of the internal os overlying the cervix from women at term undergoing elective surgical delivery in the absence of labour, had higher PGDH activity than chorion collected from an area adjacent to the placenta, or an intermediate location. At the time of labour, however, the level of PGDH activity in cervical chorion decreased dramatically, to the extent that they were significantly lower than other areas of the uterus.[39] Reduced PGDH activity in cervical chorion may allow

PGE_2 generated in the amnion or chorion to pass to the cervix and help promote cervical effacement and dilatation.[1]

1.4.4 The role of corticotropin-releasing hormone

Corticotropin-releasing hormone, a 41-amino acid peptide hormone, was first identified in the hypothalamus in 1981 and was named for its ability to stimulate the secretion of ACTH from the pituitary.[40]

Hypothalamic CRH is one of the principal components of the adaptational response to stress in humans, the so-called "fight or flight" reaction.[41] In 1982, CRH was identified in the human placenta and two years later high concentrations of this hormone were reported in the plasma of women during the third trimester of pregnancy.[42]

Placental CRH is expressed in primates only and has been localised to the syncytiotrophoblast, chorion trophoblasts, amnion epithelium and decidua.[43] Over the past 10 years there has been considerable interest in the possible role that CRH plays in the regulation of human pregnancy and parturition.[2] In pregnant women, plasma concentrations of CRH are low during the first trimester and rise exponentially from midgestation to reach levels of up to a 1000 times more than in the nonpregnant state during the last six to eight weeks of pregnancy.[41,44] Plasma levels of CRH increase even more dramatically during labour.[44] The rate with which plasma CRH rises throughout pregnancy varies considerably between individual women and is proposed to correlate with the timing of delivery[16] (discussed below). Placental CRH is secreted into both the fetal and maternal circulations.[41]

The biological activity of CRH in maternal plasma is inactivated by its binding to a high-affinity binding protein, the CRH-biding protein (CRH-BP), produced in the liver and placenta.[45] CRH-BP is also present in fetal plasma as well as in amniotic fluid.[46] Binding to CRH-BP blocks the ability of circulating CRH to induce ACTH release from the anterior pituitary and it inhibits the stimulatory effect of CRH on uterine prostaglandin production.[2] During most of pregnancy, CRH is present at concentrations that greatly exceed that of CRH and only begin to fall by week 36 of normal gestation, which coincides with the rapid rise in maternal plasma CRH.[47,48] It is only in the final three weeks of pregnancy that CRH is present at a high enough concentration to saturate CRH-BP, resulting in free, biologically active CRH in maternal plasma.[47]

Regulation of placental CRH output is multifactorial, and a variety of factors shown to stimulate hypothalamic CRH release, exert similar effects on placental CRH.[5,41] Progesterone and nitric oxide decrease the release of placental CRH whereas neuropeptides, prostaglandins, oxytocin, catecholamines and cytokines up-regulate CRH gene and protein expression.[5]

The regulation of CRH expression in the hypothalamus is quite different from placental regulation in that glucocorticoids inhibit hypothalamic CRH secretion.[49] Placental CRH stimulates the fetal HPA-axis to produce DHEAS, cortisol and cortisol sulfate, which, returning to the placenta through umbilical circulation, are capable of further stimulating placental CRH production and thus creating a positive feedback loop.[47,49] Once established, this positive feedback loop is progressively amplified and drives the fetal-placental unit towards fetal maturation and delivery.[47] This was demonstrated *in vivo* by Marionini *et al.*, when women receiving antenatal glucocorticoids to promote fetal lung maturation had increased levels of placental CRH in maternal and fetal plasma as well as in amniotic fluid than women who did not receive steroids.[50] They also found that

levels of ACTH and cortisol was lower in the maternal and fetal plasma and in the amniotic fluid. This is consistent with the negative feedback action of glucocorticoids on the maternal HPA-axis, and on the fetus, after placental transfer of the glucocorticoid. Fortunately, stimulation of placental CRH output by external glucocorticoids appears to be transient.[2] This phenomenon could be the result of increased prostaglandin output through up-regulation of PGHS and down-regulation of PGDH by placental CRH.[36]

An important question at this point is: what is the biological role of CRH during pregnancy and labour?

Although there is not yet a clear answer, several possibilities exist.

- Placental CRH, via the umbilical vein, stimulates fetal pituitary ACTH release, which in turn stimulates secretion of fetal adrenal cortisol.[18] Cortisol plays an important role in the maturation of fetal lungs and other organs, necessary for extrauterine life, and stimulates further placental CRH output.[49]
- Corticotropin releasing hormone stimulates the production of prostaglandins in the placenta, decidua and fetal membranes, *in vitro.*[45] Prostaglandin $F_{2\alpha}$ and PGE_2, in turn, can induce the synthesis of CRH by the human placenta.[44]
- Corticotropin-releasing hormone is a potent vasodilator and may act as a local regulator of placental vascular tone by reversing the vasoconstrictor effects of $PGF_{2\alpha}$.[51] This action, following the stimulation of the fetal HPA-axis, may be one way the fetus can respond to an adverse intrauterine environment, such as acute hypoxaemia or intra-uterine infection.[2] Wallace and Baker reported that in pregnancies complicated by increased placental vascular resistance, betamethasone administration was associated with decreased placental resistance.[52]
- Production of DHEAS from the fetal adrenal is another proposed action of CRH during parturition.[18] Thus, there may be a functional link between

placental CRH and the fetal adrenal zone for the production of DHEAS, as the placenta cannot directly synthesise estriol and depends on the fetal adrenal for its predominant precursor.[44] This positive loop may be responsible for the production of estrogen at term, which probably plays a major role in the mechanism of labour, through the stimulation of oxytocin, oxytocin receptors, gap-junction formation and prostaglandin synthesis.[41]

- There have been suggestions by some researchers that CRH has an effect on myometrial tone.[20] Studies to support this view, show that CRH can modulate myometrial contractility by enhancing the actions of uterotonins, such as oxytocin[53] and $PGF_{2\alpha}$,[54] although is has no direct stimulatory action itself.[20]
- Challis *et al*[2] and Grammatopoulos and Hillhouse[44] have speculated that during gestation, CRH acts as a myometrial relaxant, rather than a uterotonin through its binding to specific CRH-receptors in the myometrium.

1.4.5 Myometrial CRH-receptors and control of uterine contractility

Corticotropin-releasing hormone mediates its actions by binding to specific high-affinity CRH-receptors identified in the human myometrium.[20,55] The CRH-receptor exists in two subtypes, namely CRH-R1 and CRH-R2,[2] which suggests that CRH, acting via these different subtypes, is able to exert different actions on the pregnant myometrium.[44] The R1-receptor predominates in the myometrium, fetal membranes (chorion and decidua, but not the amnion) and placenta, while CRH-R2 expression seems to be limited to the myometrium.[56] These receptors shift the equilibrium for binding away from the circulating CRH-BP towards the myometrial receptors.[57] The CRH-R1 receptors are linked to the adenylate cyclase system through $G_{\alpha s}$-regulatory proteins, which stimulate cAMP output by myometrial cells, causing relaxation.[44] Grammatopoulos and Hillhouse demonstrated that human CRH was able to partially inhibit PGE_2 production in

myometrial cells, with the PGI_2-pathway remaining unaffected by CRH.[58] This action did, however, not involve the suppression of cyclooxygenase-2 (PGHS-2), suggesting that prostaglandin synthesis is blocked by CRH in the myometrium only, and that CRH may in fact play an important role in the maintenance of uterine quiescence during pregnancy.[2,58]

As term approaches, it appears that the relaxing effect of CRH on the myometrium is diminished, probably because there is a reduced coupling of the CRH-receptor $G_{\alpha s}$ regulatory protein complex with the catalytic component of adenylate cyclase.[57] Oxytocin may well play a role in this phenomenon. At term, oxytocin up-regulates PKC which phosphorilates CRH-receptor proteins, resulting in their desensitisation and subsequent loss of inhibitory influence.[59] Stevens *et al.* demonstrated that levels of CRH-R1 mRNA were significantly increased in the lower uterine segment, but not the fundus, of patients during term and preterm labour. They also found an increasing trend in CRH-R1 mRNA between 32 and 39 weeks in the absence of labour.[20] Hence, it was suggested that CRH may have a dual function during labour: contributing to the regionalisation of uterine activity during labour, through a relaxing effect on the lower uterine segment and stimulating the fundus by up-regulating prostaglandin synthesis from the chorion and decidua.[2,20]

1.4.6 The role of CRH in the onset of parturition

Grammatopoulos and Hillhouse[44] formulated the following hypothesis for the role of placental CRH in the onset of human parturition, based on their own data as well as that of others:

- Placental CRH is inactivated in early pregnancy due to its binding to the circulating CRH-BP. Linton *et al.* found in an *in vitro* study, that about 8% of CRH remain unbound and a total reduction in bioactivity would therefore not be expected.[60] This action protects the maternal pituitary from placental, but

not hypothalamic, CRH, preserving the normal HPA-axis function. However, CRH-BP levels do not seem to vary between women with preterm, term and post-term pregnancies,[16] leaving free CRH to bind to tissue receptors after plasma CRH concentrations has reached saturation levels for binding to CRH-BP.[61] This suggests that in women with higher than normal levels of CRH, preterm delivery may be anticipated.

- Later in pregnancy, after the switching of the myometrial CRH-receptors to a high-affinity state, CRH binds to the myometrium, generating cAMP and inhibiting PGE_2 synthesis, causing relaxation of the pregnant myometrium.[44]
- As term approaches, up-regulation of oxytocin-receptors occurs, leading to a PKC-induced switch of the CRH-receptor back to a low-affinity state. It has been suggested that there are multiple CRH-receptor isoforms and that only some of them are sensitive to the actions of oxytocin.[62] This action reduces intracellular cAMP expression, causing an increase in myometrial excitability and the effect is amplified even more by the down-regulation of the CRH-receptors ($G_{\alpha s}$) in the fundus at term.[44]
- These changes also facilitate the actions of uterotonins, such as oxytocin and $PGF_{2\alpha}$, pointing to a dual role for CRH during human gestation and labour.
- Fairly high concentrations of CRH may be required for these changes that are necessary for activation, and therefore the decrease in CRH-BP towards term would be an important factor in the development of this mechanism.[44]
- These events all come together as a positive feedback loop of hormonal signals, which are progressively amplified and the only way that these loops can be broken is by the delivery of the fetus and the placenta (Figure 1.5).[47]

The challenge for investigators will now be to test this hypothesis as complications in pregnancy, such as preterm labour or pre-eclampsia could result from various abnormalities in the CRH system. The ideal would be *in vivo* experiments in patients with normal and abnormal pregnancies, but such

research is not feasible for ethical reasons. Animal experiments, even on primates, would not be helpful either, because of the different mechanisms of labour between the species. The mystery of human parturition may therefore best be resolved through testing at cellular and molecular level.[44]

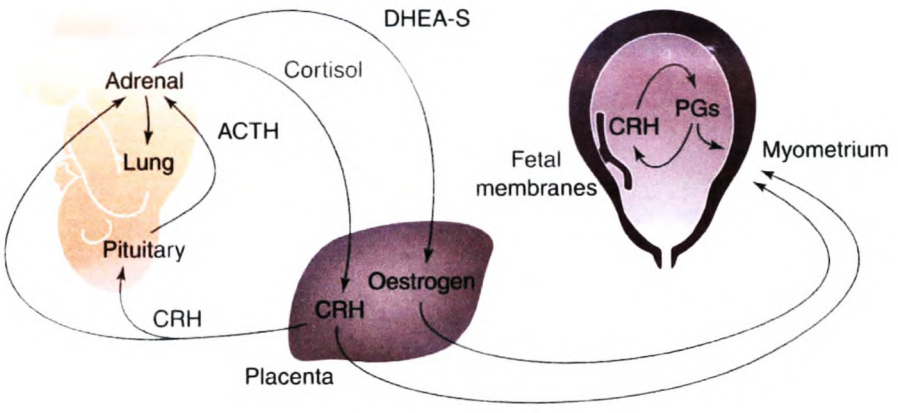

Figure 1.5 Interacting positive-feedback hormonal loops in the fetal, amniotic and maternal compartments that may promote the progression of fetal maturation and initiation of parturition in humans.

ACTH = adrenocorticotrophin
CRH = corticotropin-releasing hormone
DHEA-S = dehydroepiandrsterone sulphate
PG = prostaglandins

1.4.7 The concept of a "placental clock"

McLean *et al*. assessed the serial changes in the relative concentrations of maternal plasma CRH and CRH-BP during pregnancy and related it to the subsequent timing of delivery.[16] A total of 485 pregnant women were recruited at their first antenatal visit and plasma samples were obtained prospectively during the second and third trimesters. Each woman provided between one and four samples (median = 2) at four- to six-week intervals. Plasma CRH levels were found to be significantly higher in those women who subsequently delivered preterm and significantly lower in those who delivered post-term (Figures 1.6 a – c).[16] These differences were already evident at mid-gestation and may be an indication of progressive maturation of the placenta, established already early in pregnancy.[47] The concentrations of CRH-BP was present in excess of CRH throughout most of pregnancy, but the exponential rise in plasma CRH resulted in an equivalence point being reached approximately 20 days before spontaneous term delivery, which is consistent with the normal course of events.[16,47]

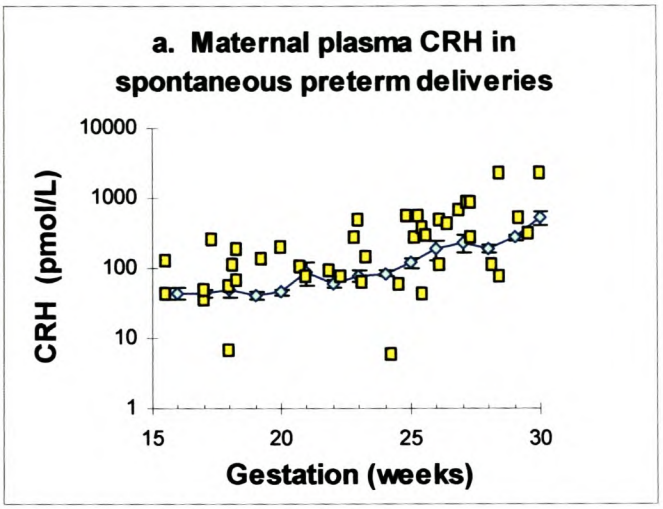

Figure 1.6a Maternal plasma CRH-concentrations (yellow) throughout mid-gestation in women whose pregnancies ended in spontaneous preterm labour, as compared to women who delivered at term (blue). (From Mclean *et al.*[16], used with permission.)

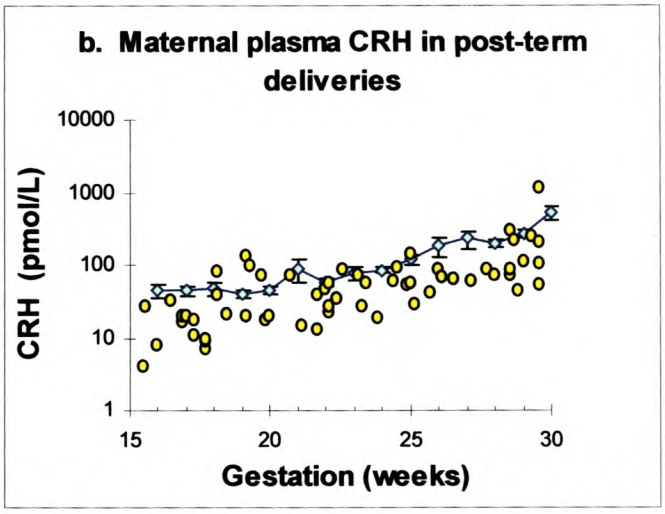

Figure 1.6b Maternal plasma CRH-concentrations (yellow) throughout mid-gestation in women who delivered post-term, as compared to women who delivered at term (blue). (From Mclean *et al.* [16], used with permission.)

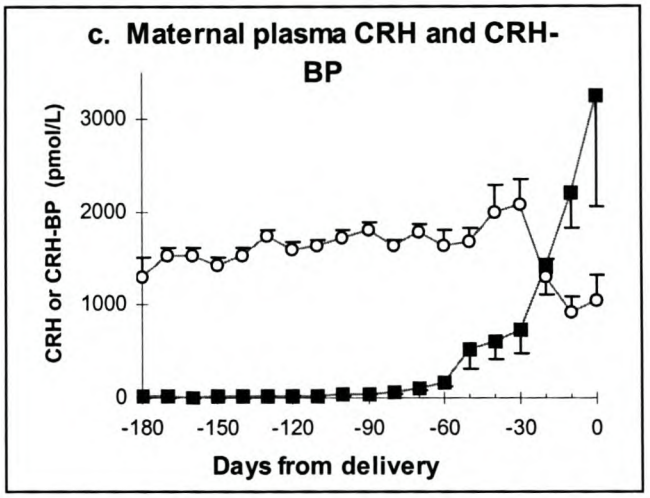

Figure 1.6c Comparison of maternal plasma concentrations of CRH (■) and CRH-BP (○) during the last 180 days of pregnancies ending in spontaneous term labour. (From McLean *et al.*[16], used with permission.)

By virtue of these results a proposal was made for the existence of a "placental clock", as the patterns of plasma CRH were associated with the timing of delivery, both early and late.[16] The idea of a placental clock in the timing of human parturition is very inviting, as it may well enable the prediction of possible preterm deliveries, raising the opportunity to educate women on their increased risk of PTL, early warning signs and maybe even early intervention. This concept also challenges the notion that the duration of gestation is determined only by events late in pregnancy. In support of this hypothesis is the finding that maternal plasma α-fetoprotein (AFP) concentrations are also associated with the timing of delivery, although less strong than CRH.[63]

The rate of increase in plasma CRH determines when saturation of CRH-BP will be achieved, resulting in free, biologically active CRH in the maternal

circulation.[47] An important concept contained in the placental clock hypothesis is that, whether it is through the action of CRH or by other mechanisms, parturition results from a process begun very early in pregnancy. The placental clock is, of course, not the sole determinant of the timing of delivery in a given pregnancy. Even before conception, genetic predisposition, socioeconomic factors, maternal medical history and pathological events in the mother or fetus, may influence the duration of a future pregnancy.[46] It has been found that individual women tend to have the same gestational duration in subsequent pregnancies, making a history of a previous preterm delivery the single most important predictor of PTD in an index pregnancy.[64] Also in support of possible genetic influences, is the fact that women who were born prematurely themselves, are more prone to deliver preterm (intergenerational, mother-to-daughter association).[65,66]

1.5 CONCLUSION

The physiological processes involved in the onset of parturition in human are still not clearly defined. There is, however, evidence to conclude that the fetus does in fact play a role in the initiation of the process and does indeed makes good sense. It is often observed that pregnancies associated with conditions detrimental to the fetus, such as placental insufficiency or intra-uterine infection, are associated with increased likelihood of preterm delivery. This is supportive of the notion that the fetus can initiate parturition if its survival *in utero* is threatened.[47] There is no neural connection between mother and fetus and communication must therefore occur by hormonal signals, the two possible vectors being the umbilical blood and the amniotic fluid. Many of the hormones involved in regulation parturition are synthesised by the placental trophoblasts situated at the interface between the fetal and maternal blood circulations.[47]

Preterm labour is not necessarily an acceleration of the normal physiological processes leading up to parturition and those preterm deliveries caused by

infection or placental abruption may be through alternative mechanisms.[47] Two recent studies concluded that women with infection-related (chorioamnionitis) PTL had significantly lower levels of plasma CRH than women presenting with idiopathic preterm labour ($p < 0.005$ in both studies).[67,68] Warren *et al.* found the levels of plasma CRH of those women with infection-related PTL to be similar than women with normal pregnancies at the same gestational age.[68]

Idiopathic PTL would more likely be associated with an acceleration of the normal course of events, resulting in the elevated levels of plasma CRH. Several studies that support the hypothesis of abnormally elevated CRH levels in women at risk for PTL have been conducted (discussed in Chapter 2), but the applications of CRH research in clinical practice, is still remote. Ongoing research may lead to improvements in our ability to predict and even prevent preterm birth, which is the leading cause of perinatal mortality and morbidity around the globe.

CHAPTER 2: PRETERM LABOUR AND DELIVERY

2.1 INTRODUCTION

Preterm birth, generally defined as delivery before 37 weeks gestation, occurs in approximately 5 – 10% of all pregnancies and has not, despite many efforts, shown any decrease in the past 30 years.[36,69] Due to the increasing rate of multiple births through fertility treatments and increased maternal and fetal surveillance during gestation, often resulting in earlier deliveries, the overall rate of preterm delivery (PTD) has, in fact, risen slightly over the past two decades.[70,71]

Preterm birth is more correctly described as a syndrome, representing a myriad of causes, which may also differ at different gestational ages.[5] Preterm delivery and low birthweight (LBW) is the leading cause of perinatal mortality in the United States (US)[72] and the second largest cause of perinatal death in the Western Cape.[73] In certain populations, the overall rate of PTD is even higher than 10%, with South Africa being no exception. In our population PTD occurs in 20.3% of pregnancies (Tygerberg Hospital database, unpublished data).

Preterm prelabour rupture of membranes (PPROM) and spontaneous PTL account for about 80% of preterm deliveries with the remaining 20% being iatrogenic, requiring medical intervention for maternal (e.g. pre-eclampsia) or fetal reasons.[2,74] It is estimated that 30 – 40% of all preterm deliveries are due to underlying infection and that 40 – 50% are idiopathic.[2,75] Very-low-birthwight (VLBW) infants, weighing between 500 and 1 499 grams, account for about 1% of all live births and 60% of all neonatal deaths.[70]

Overall, preterm birth is still associated with 70% of neonatal deaths[2], even though the rate has dropped dramatically over the past 40 years, mainly because of advanced high technology and neonatal care. Today, in developed countries, even extreme premature infants (born at less than 26 weeks of gestation), have a chance to survive. Rates of survival for babies born at tertiary perinatal institutions in the US increase significantly with each week of gestational age from 22 weeks (0 - 21.4%) to 26 weeks' gestation (75 – 93%).[76] Although many preterm babies survive today, up to 75% of neonatal morbidity is still associated with prematurity.[70]

In the USA, the annual cost of caring for preterm babies has been estimated at around $8 billion.[36] This figure does not take into account the amount of emotional and psychological strain on the family, nor the long-term costs required for chronic care for those who need it.[2] For families from a disadvantaged background, the emotional strain may be even greater, as they are often not in a position to provide extra or special care for those babies.

Preterm children have an increased incidence of neurosensory conditions (e.g. cerebral palsy, blindness and deafness), neurological handicap and pulmonary disorders.[5] At school age, preterm children are more likely to have poorer cognitive function and academic performance[77] and learning problems at school seem to persist into adolescence, which are even apparent in children with normal intelligence and no neurological impairment.[78] It has also been reported that fewer children who weighed less than 1000 grams at birth graduated from high school.[77]

Hack *et al*. undertook a longitudinal study of VLBW children (weighing less than 1500 grams at birth) born between 1977 and 1979, which they compared to normal birthweight children. They first reported their outcomes at eight years of age and recently reported their outcomes at 20 years.[77] Significantly fewer

preterm young adults graduated from high school and significantly fewer men in the VLBW-group enrolled in college or university. The preterm group had a lower mean IQ (87 vs. 92) and lower academic achievement ($p < 0.001$ for both comparisons). Preterm young adults had significant more chronic conditions than the control group, which was largely attributable to the higher rates of neurosensory impairment ($p < 0.001$) and subnormal height ($p = 0.004$). In terms of alcohol and drug use, the preterm group appeared less likely to engage in high-risk behaviour. The men were less likely to have had contact with the police and women were less likely to have engaged in sexual activity, become pregnant or delivered a baby. The rates of smoking and criminal behaviour were similar to both groups.[77]

2.2 MARKERS OF RISK FOR PRETERM DELIVERY

Risk factors for PTL have been classified as avoidable or unavoidable (summarised in Table 2.1), which is valuable in the sense that, if avoidable risk factors can be detected and addressed (ideally, prior to conception), there is a significant chance that perinatal morbidity and mortality can be reduced.[79,80,81]

Table 2.1 Risk factors for preterm labour and delivery

Unavoidable Risk Factors

Prior history of preterm delivery

Black race

Cervical dilation, effacement, surgery or abnormality

Maternal employment, e.g. exposure to teratogens

Socioeconomic status

- Abuse
- High stress levels
- Age < 18 years or primigravidae ≥ 35 years
- Poverty

- Low prepregnancy weight for height
- Unmarried

History of infertility

Abruptio placentae

Avoidable Risk Factors

Prior obstetric complications

Maternal disease, e.g. diabetes mellitus, hypertension, urinary tract infection

Reproductive tract infection

Uterine abnormalities or fibroids

Smoking, especially ≥ 10 cigarettes per day

Alcohol or substance abuse

Short interpregnancy interval

Maternal anaemia

Some of these risk factors are reviewed below.

2.2.1 PRIOR HISTORY OR PRETERM BIRTH

A previous history of preterm labour and delivery is a significant risk factor for future preterm delivery.[82] Recently, the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network conducted the "Preterm Prediction Study" and documented that a prior spontaneous PTD carries a 2.5-fold increase in the risk of PTD in an index pregnancy, compared to those with no previous PTD (21.7% vs. 8.8%; p = 0.001).[64] A previous PTD was also associated with a 10.6-fold increase in the relative risk (95% CI 2.9 – 38.8) to deliver before 28 weeks in the current pregnancy (2.5% vs. 0.23%; P < 0.001).

The cause(s) of the first PTL or delivery for an individual woman, unfortunately, usually remains a mystery.

2.2.2 MATERNAL STRESS

"...the same soul governs the two bodies. One will, one supreme desire, one fear that the mother has, or mental pain, has more power over the child than the mother, since, frequently, the child loses its life thereby..."

from: Leonardo da Vinci, the Anatomist, 1930 [83]

Stress can be defined as a psychophysiological consequence of any event challenging homeostasis and therefore an organism's capacity to cope, while anxiety is considered the psychological consequence of exposure to real or imagined stress.[84,85,86]

Stressful experiences include major life events, trauma, abuse and sometimes even the environment in the home, workplace or neighbourhood.[87] Stress can be acute (in the sense of the "fight-or-flight" reaction or a major life event, such as the death of a spouse and even pregnancy), or it can be chronic (the cumulative load of minor day-to-day stressors) and both can have long-term consequences.[87] Both physical and emotional stressors set into motion central and peripheral responses designed to preserve homeostasis (Table 2).[88,89]

Centrally, there is a facilitation of neural pathways with concurrent inhibition of pathways subserving vegetative function, such as feeding (e.g. loss of appetite).[85] Peripheral changes promote redirection of energy, with the subsequent direction of oxygen and nutrients to the central nervous system and stressed sites. Increased cardiovascular tone leads to increased heart rate and subsequent elevated blood pressure, while increases in respiratory rate,

gluconeogenesis and lipolysis all promote availability of vital substrates.[85] The result of peripherally mediated restraint of growth and reproduction is the availability of energy that could be used more efficiently in the adaptive response to stress.

Table 2.2 Behavioural and physical adaptation during stress

Behavioural adaptation

- Adaptive redirection of behaviour
- Acute facilitation and inhibition of non-adaptive neural pathways
  - Increased arousal and alertness
  - Increased cognition, vigilance and focused attention (including appropriate aggression)
  - Suppression of feeding and reproductive behaviour
  - Containment of stress response

Physical adaptation

- Adaptive redirection of energy
  - O_2 and nutrients directed to central nervous system and stressed body sites
  - Altered cardiovascular tone, increased blood pressure and heart rate
  - Increased respiratory rate
  - Increased gluconeogenesis and lipolysis
  - Detoxification from toxic products
  - Inhibition of growth and reproductive systems
  - Containment of the stress response, inflammatory and/or immune response

Two factors largely determine individual response to stressful situations: the way a person perceives a situation and the person's general state of health, which is

determined not only by genetic factors, but also by behavioural and lifestyle choices.[87] Perceiving a situation as a threat, either psychological or physical, is crucial in determining the behavioural response – fleeing, fighting or trembling with fear – and therefore the physiological response: calmness or heart palpitations and elevated cortisol levels.[87] How one perceives a stressful situation will thus also determine one's ability to adjust and cope with repeated episodes of the same stressor.

2.2.2.1 Physiologic response to stress

The neuroendocrine and immune systems play a major role in response to stress with the principal effectors being the CRH and locus ceruleus-norepinephrine (LC-NE)/autonomic (sympathetic) nervous systems, regulating the peripheral activities of the HPA-axis and the systemic/adrenomedullary sympathetic nervous systems, respectively.[85,86] In addition to the hypothalamus, the CRH system is also found in the lateral bed nucleus of the central nucleus of the stria terminalis and the central region of the amygdala.[90] To a smaller degree, there are CRH cells in the lateral hypothalamus, prefrontal and cingulated cortex in the brainstem.[90] Moderate doses of CRH sets into motion a coordinated series of physiological and behavioural responses to stress, including activation of the HPA-axis. CRH acts at the anterior pituitary to trigger the release of ACTH, which, in turn, acts on the adrenal cortex to stimulate the synthesis and release of glucocorticoids, resulting in the events summarized in Table 2.[85,91] The HPA-axis, as mentioned previously, is subject to negative feedback control by ACTH and cortisol.

The LC-NE/sympathetic systems are located in the brainstem and activation leads to the release of norepinephrine, resulting in enhanced arousal and vigilance as well as increased anxiety.[85] Inhibition of immune functioning by glucocoticoids is also a result of the response to stress, which may be a

compensatory action of the HPA-axis to mitigate other physiological effects of stress.[91] However, certain cytokines, especially tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1) and IL-6, as well as several eicosanoids and platelet-activating factors, also activate the HPA-axis.[85,86]

2.2.2.2 Allostasis and allostatic load

Homeostatic systems, such as blood pH and body temperature, must be maintained within narrow ranges, whereas allostatic (adaptive) systems have much broader boundaries.[87] Allostasis refers to the ability of our bodies to achieve stability through change (increase or decrease vital functions to a new steady state on challenge), in part by increasing HPA-axis and sympathetic activity to promote adaptation and reestablish homeostasis.[92] Allostatic systems respond to a physical state (e.g. awake, asleep, exercising), and enable one to cope with situations such as extremes in temperature, danger or infection. At the core of the human body's response to a challenge is the ability to turn on the appropriate allostatic response, initiating a complex adaptive pathway and is shut off again once the challenge or threat has passed.[87,90] The most common allostatic responses involve the sympathetic nervous systems and the HPA-axis.[87] However, should the allostatic systems remain active, there is overexposure to stress hormones, and this phenomenon is referred to as "allostatic load".[92] Such exposure over prolonged periods of time can cause "wear and tear" on tissues and accelerate pathophysiology, resulting in premature damage of vital organs.[87,90]

Four situations are associated with allostatic load:[87]

The first and most obvious situation is overstimulation by frequent stress, resulting in excessive exposure to stress hormones. Secondly, the lack of adaptation to repeated stressors or challenges (e.g. public speaking) will also cause prolonged exposure to stress hormones. In the third place is the inability to

shut off allostatic responses once the challenge has passed. For example, women with a history of depression have decreased bone mineral density, because the allostatic load of chronic elevated serum cortisol concentrations inhibits bone marrow formation.[93] The fourth type of allostatic load occurs when one or more system is inadequate in responding to a specific stressor, which will then trigger increased activity in other systems as compensation. (e.g. inflammatory cytokines).[90]

Exaggerated anticipation of negative events that may or may not occur, can also contribute to allostatic load.[90] Anticipatory anxiety can drive the secretion of CRH, cortisol and epinephrine and therefore, prolonged anxiety and anticipation are likely to result in allostatic load.[90] In addition, memories of a traumatic event (e.g. sexual abuse), as is a common feature in post-traumatic stress disorder, can also produce a form of chronic stress and trigger prolonged physiological responses.[91] Integral to the overall notion of allostasis and allostatic load, is the way people cope with stressful situations (Figure 2.1). Excessive smoking and alcohol use, an unbalanced, high-fat diet ("comfort food") and a lack of physical exercise, are known to exacerbate the effects of chronic stress.[87]

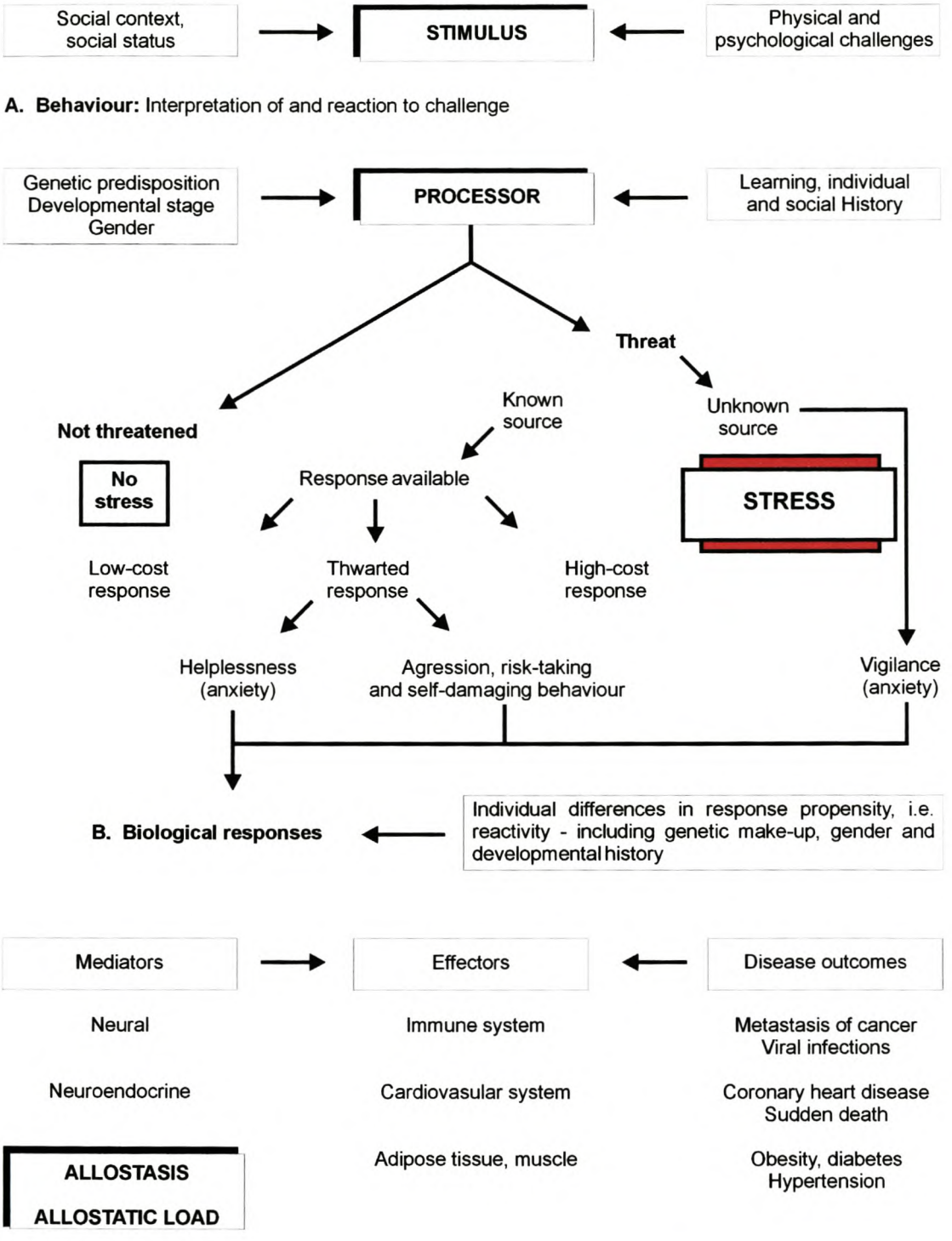

Figure 2.1 General sequence of events that occur under stressful conditions, resulting from the interpretation of the situation. McEwen et al.[92]

2.2.2.3 Antenatal maternal stress

Antenatal stress is perhaps a common theme that features in individual as well as population based risk factors for PTD.[86] Developmental neurosciences support a model of development, where the antenatal environment plays a crucial role in the development of the fetus.[86] An optimal environment would be expected to be beneficial and a hostile one, as those affected by stress, could have a deleterious effect on fetal development.[94] A number of epidemiological studies support the hypothesis that maternal psychosocial stress is an independent risk factor for PTD and LBW.[84] Lou *et al*. conducted a prospective, population-based study where 3021 pregnant women completed a questionnaire on environmental and psychosocial factors. They compared the 70 "most stressed" women to 50 controls. Perceived stress significantly and independently affected gestational age ($p = 0.04$) and birthweight. Smoking also significantly contributed to LBW and the babies whose mothers' experienced antenatal stress had a smaller head circumference and a sub-optimal neurological score.[83] In another prospective study, Wadwha *et al*. tested the influence of maternal antenatal stress (episodic and chronic stress, response to stress and pregnancy-related anxiety) on birth outcomes after controlling for medical antenatal risk factors. Independent of biomedical risk, maternal stress was significantly associated with lower birthweight and earlier gestation at delivery ($p < 0.01$).[95]

There is a wide disparity in the rates of PTD between socioeconomic advantaged and disadvantaged women when comparing age, marital status, education, occupation and income.[86] It was found that behavioural factors such as availability and utilization of antenatal care, nutrition, physical activity and high-risk behaviour (smoking, alcohol use and drug use) only play a limited role in this inequality.[96] Antenatal stress, therefore, remains a viable explanation for PTD

as there is a strong association between low socioeconomic status and psychological stress.[86]

A perhaps overlooked cause of stress is the experience of racism, maybe because "it is not supposed to happen" any more. Black women are two to three times more likely than white women to deliver preterm.[97] This disparity remains even after controlling for sociodemographic and behavioural factors as well as access to antenatal care.[71,98] There are speculations that genetic differences between races may account for these differences, but this is, however, unlikely.[86] Studies of genetic differences along racial or ethnic characteristics suggest approximately 85% variability within the same race and only 6 – 9% between different races.[99] Also, among black immigrants in the US, the incidence of diverse health outcome, including PTD, is positively associated with the duration of their stay in America, even after controlling for socioeconomic variables.[100] One observer states that "growing up as a woman of colour in the US, is somehow 'toxic' to pregnancy."[97] The same may be true for South Africa, as our democracy is a lot younger than that of the US and the unhealed wounds from our past is still very much a reality.

Maternal antenatal stress is therefore a credible factor in producing, and even increasing, vulnerability for maternal-placental-fetal neuroendocrine and/or infection-related immune pathophysiology.[86]

Viable explanations as to how exposure to stressful conditions can thus influence pregnancy outcome are through either the activation of the HPA-axis, resulting in increased cortisol concentrations, or by the mother engaging in high-risk behaviour (excessive smoking, alcohol and substance abuse) as a coping mechanism.

The suggestion that there is a link between maternal stress and PTD is supported by the increased prevalence of PTD among women who are unmarried, of poor socioeconomic background or who were subjected to major stressful events, which include physical and sexual abuse.[101] Having more money or a higher education probably has no direct effect on the duration of a pregnancy. Socioeconomic disadvantage is, therefore, more likely to be an indirect determinant of PTD, leading to unhealthy behaviour, exposure to stress and psychological reactions to stress that can shorten gestation.[102] Another factor that may predispose a woman to PTD is her attitude towards the pregnancy and the baby. De Muylder *et al*. concluded that women with a "poor investment in pregnancy" were significantly more likely to deliver preterm.[103] It is a quite logical conclusion that a woman who is, for example, not married, of low socioeconomic status and being beaten by her partner, will not feel very positive at the prospect of having to raise a child under such circumstances.

2.3 ACTIVATION OF THE MATERNAL AND/OR FETAL HPA-AXIS

Since maternal stress is characterized by an increase in CRH and cortisol through the activation of the maternal HPA-axis, early activation of the fetal HPA-axis may occur and result in PTL and even delivery.[16] Normally, maternal cortisol that crosses the placenta is converted to inactive cortisone through the action of placental 11 β-HSD-2, but excessive exposure to both endogenous and exogenous cortisol has been found to inhibit the actions of this enzyme[15], leaving free cortisol to activate the fetal HPA-axis. Premature activation will enhance the production of estrogens, which in turn, interacts with the myometrium and may lead to premature activation of the parturition process (Figure 2.2).[79]

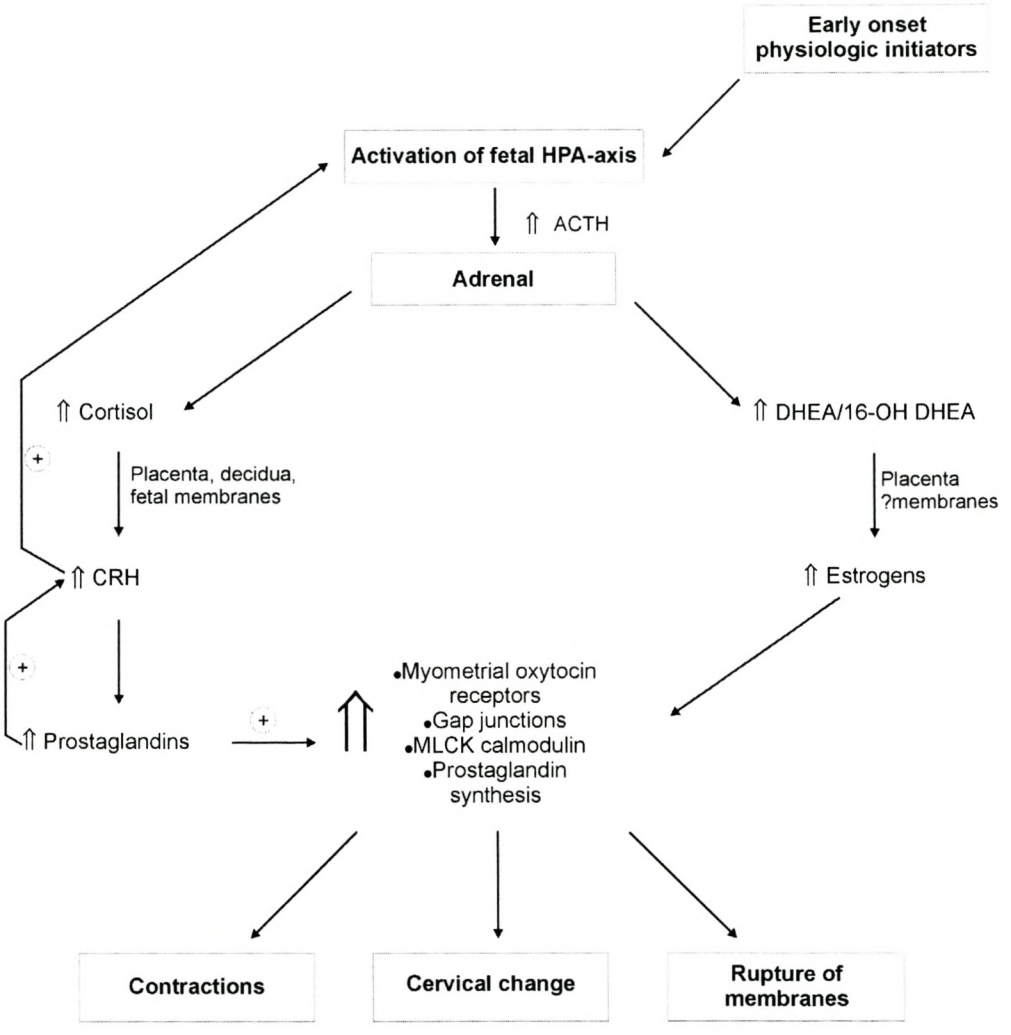

Figure 2.2 The role of estrogens and cortisol in the activation pathway of the maternal and/or fetal HPA-axis, leading to uterine contractions, cervical changes and/or rupture of fetal membranes. Adapted from Lockwood *et al.*[79]

Several studies challenged the hypothesis that premature elevation of maternal plasma CRH-concentration may be a marker of impending preterm birth.[67,104,105,106,107] In a recent study, Wadhwa *et al.* found that in a sample of 63 women, those who delivered preterm and whose babies weighed less than 2 500 grams had elevated levels of plasma CRH at 28 – 30 weeks gestation ($p = 0.001$ on both accounts).[104] Even after adjusting for antenatal risk factors, the difference remained significant. Another study enrolled 233 women with a diagnosis of spontaneous PTL (excluding other complications such as pre-eclampsia, multiple gestation and clinical infection), between 24 and 36 weeks gestation to determine whether elevated CRH-levels could predict which of those women will deliver within 24 hours.[67] Overall, plasma CRH-concentrations were significantly higher in those women who gave birth within 24 hours of admission ($p < 0.05$), but this difference was only present between 28 and 36 weeks and not between 24 and 28 weeks' gestation.[67]

In a "behaviour in pregnancy" study, Hobel *et al.* prospectively followed up 524 women of low socioeconomic background at 18 – 20, 28 – 30 and 35 – 36 weeks gestation. Data on perceived stress and anxiety levels were collected as well as maternal CRH plasma levels.[105] Blood samples were available for only 18 women who delivered preterm and were matched to 28 controls. The preterm group has significant higher levels of CRH at 18 – 20 as well as 28 – 30 weeks, but the difference in stress levels did not reach statistical significance. However, there was a significant association between psychosocial stress measured at 18 – 20 weeks and significantly elevated CRH levels at 28 – 30 weeks.[105] Stress levels also predicted significant changes in CRH levels between 18 – 20 and 28 – 30 weeks. There was no overlap in CRH levels between the preterm and term groups, suggesting that gene expression may occur even before 28 weeks and is consistent with the "placental clock" hypothesis.[16,105] They further suggest that maternal stress could be a trigger for this biological clock.

The fact that PTD has a multifactorial etiology, may explain why a single sample of maternal plasma CRH has such a low positive predictive value. In a prospective observational study of 1047 pregnant women, elevated levels of CRH produced PTD with a positive predictive value of 3.6% and a negative predictive value of 99.6%.[106] McGrath *et al.* analyzed two to four plasma samples each for 305 pregnant women to determine whether the trajectory of increase of placental CRH provided more information on risk for PTL than did a single sample.[107] They compared the CRH levels of women who delivered at term with those who had iatrogenic and idiopathic preterm deliveries. Women with subsequent iatrogenic PTD had a similar mean concentration of CRH than those who delivered at term, but once in labour, the rate of rise in CRH was significantly greater. In the spontaneous PTD group the mean CRH concentration was significantly higher than both the term and iatrogenic groups, but the rate of rise was similar to that of the term group. This study once again confirms that women who are destined to deliver preterm have elevated levels of CRH that are already evident early in gestation. Whether this evidence, and if so, how, can be implemented in clinical practice in order to identify women at risk for PTD, remains to be determined.

2.4 INFECTION

For more than 35 years, multiple studies from different disciplines (e.g. epidemiology, microbiology, biochemistry and maternal-fetal-medicine) have shown an association between infection and PTD.[79,81,108] It is estimated that genital tract infections and intrauterine infection contribute to between 40 and 50% of all preterm deliveries, especially those that occur before 30 weeks of gestation.[36,79,109] There is evidence suggesting that infection that leads to PTD is already present at a very early gestation and can remain undetected for several weeks prior to PTD.[110] The epidemiologic profile of women at risk for PTD overlaps in some areas with that of women at risk for acquiring sexually

transmitted infections (STI's), i.e. black race, young age, low socioeconomic status and high-risk behaviour.[79]

Of the organisms that have the strongest associations with PTD are:[79,111]

- *Gardnerella vaginalis*, *Bacteroides* spp. and anaerobic bacteria associated with bacterial vaginosis (BV)
- Sexually transmitted organisms such as *Trichomonas vaginalis*, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
- Other: groups B streptococci, *E. coli*, *Klebsiella* spp., *Mycoplasma hominis* and *Ureaplasma urealyticum*.

Particularly striking is the association between BV and PTD.[112,113,114] Bacterial vaginosis is a polymicrobial, clinical condition characterised by a dramatic decrease or absence in hydrogen peroxide (H_2O_2)-producing lactobacilli and the overgrowth (100 to 1000-fold increase) of endogenous organisms, including *G. vaginalis*, *Bacteroides* and *Mobiluncus* spp. and anaerobic bacteria.[115] *M. hominis* is also strongly associated with BV.[116,117] Up to 50% of women with BV are asymptomatic (absence of foul smelling grey, homogenous discharge) and the prevalence of BV varies widely between populations studied.[118] Two independent South African studies found the prevalence of BV among pregnant women to be 29% [119] and 52% [120], respectively.

It has been reported that the presence of BV in early pregnancy (before 20 weeks), increases the risk of PTD almost two-fold.[121] Others have found that BV rarely develops as pregnancy progresses, but rather persists from the first or second trimesters in those women who deliver preterm.[122,123] Antenatal treatment of BV in order to reduce the rate of PTD has been studied in many different populations (high-risk/low-risk, developed/developing populations) with conflicting results.[72,113,119,124,125,126] These discrepancies may be because of

the differences in methodology, the different gestational ages at which treatments were prescribed as well the wide variety of treatments used. Treatments include oral or vaginal metronidazole, oral or vaginal clindamycin and oral erythromycin.

Of the different therapies used and outcomes of some of these trials are summarised below:

- Odendaal *et al.* - oral metronidazole, 400mg, twice daily x two days: found no reduction in PTD among low-risk or high-risk women with BV.[119]
- McDonald *et al.* - oral metronidazole, 400mg, twice daily x two days: reported no reduction in PTD among low-risk, BV positive women, but found a significant reduction among high-risk women.[124]
- Vermeulen and Bruinse - 2% clindamycin vaginal cream, daily for seven days: they found no reduction in PTD among high-risk women (with or without BV) or among women presenting with PTL.[125]
- Hauth *et al.* - oral metronidazole and erythromycin: a significant reduction in PTD among high-risk women with BV was demonstrated.[72]
- McGregor *et al.* - oral clindamycin, 300mg, twice daily x 7 days: found a 50% reduction in the rate of PTD among BV positive women at risk for PTD.[113]
- Carey *et al.* - oral metronidazole, 2g STAT, repeated after 48 hours: they found no reduction in the occurrence of PTD when treating asymptomatic BV.[126]

Ascending bacteria, including those associated with BV, may result in intrauterine infection, which is also quite often chronic and without clinical signs or symptoms.[127,128] Even during labour, most women who are later demonstrated to have chorioamnionitis have no symptoms other than PTL – no fever, abdominal pain or peripheral-blood leukocytosis.[128] Romero and Mazor

proposed a four-stage process by which ascending bacteria may lead to intrauterine infection:[127]

Stage 1: This stage in characterised by an overgrowth of facultative pathological organisms in the vagina and/or cervix. Bacterial vaginosis may therefore very well be an early manifestation of stage 1.

Stage 2: Once bacteria gain access to the uterine cavity they reside in the deciduas and a localized inflammatory reaction leads to deciduitis. A further extension of this reaction leads to chorionitis and the infection may also invade fetal vessels (choriovasculitis) or proceed through to the amnion (amnionitis).

Stage 3: Intra-amniotic infection is therefore the result of micro-organisms crossing intact fetal membranes, and rupture of the membranes is not a prerequisite for this infection as previously believed.[129]

Stage 4: The bacteria may gain access to the fetus through various ports of entry, resulting in localised infections such as congenital pneumonia or conjunctivitis and even bacteriaemia or sepsis. The prevalence of confirmed neonatal sepsis increase from less than 1% in term deliveries to 17% in deliveries at less than 28 weeks gestation.[130]

Of the most prevalent micro-organisms isolated from the placental membranes among women with PTD are: *U. urealyticum*, *M. hominis*, *G. vaginalis*, *E. coli*, group B streptococci, *Peptostreptococcus* and *Bacteroides* species.[129] These organisms, particularly *M. hominis*, frequently colonise the female genital tract when the vaginal ecosystem is altered by BV.[75,127] *M. hominis* has also been associated with PTD.[117] The role of *C. trachomatis* as an intrauterine pathogen has not been clarified as yet, but is had been isolated from amniotic fluid and was found to be associated with congenital pneumonia, cervicitis and PTL.[131] Results from the Preterm Prediction Study showed that women with chlamydial infection (11% overall prevalence) at 24 – 30 weeks' gestation had a three-fold increased risk of subsequent delivery before 35 weeks, were more likely to be BV positive ($p = 0.002$) and to have a short cervix ($\leq$ 25mm; $p = 0.02$).[132]

The mechanism(s) by which bacterial infections can cause PTL and delivery remains uncertain.[108] One possibility is that the organisms associated with BV may stimulate PTL by the production of high levels of arachidonic acid from membrane phospholipids through PLA_2, resulting in increased prostaglandin production.[127,133] Another proposed route is the release of inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8 and granulocyte colony stimulating factor (G-CSF), which in turn, is triggered by endo- and exotoxins released from bacterial infections.[9,134]

In addition to macrophges, IL-1 is also produced by the decidual cells in response to bacterial infection and stimulates prostaglandin synthesis, while at the same time decreasing PGDH activity.[2] IL-1 concentrations and bioactivity are elevated in women with PTL and positive amniotic fluid cultures, but not in those with PTL and sterile amniotic fluid.[135] The effects of IL-1 and TNF-α may be greatly amplified by IL-6, which is secreted by decidual and chorionic cells in response to IL-1 and TNF-α.[75,136] Interleukin-6 also increases prostaglandin production by amnion and decidual cells[137] and has been found to be predictive of approximately 50% of preterm deliveries in a cohort of women at risk for PTD.[138] Elevated cervical and serum levels of IL-6 are strongly associated with the presence of intrauterine infection[135] and is recognized as a highly accurate analyte for rapid diagnosis of subclinical infection among women with PTL.[139]

TNF-α is released by decidual cells and also stimulates decidual and amnion cells to release prostaglandins. G-CSF is produced by monocytes and attracts leucocytes into tissue.[134] Elevated maternal plasma concentration of G-CSF have been associated with PTD at less than 28 and 32 weeks' gestation, but not at 35 or 36 weeks.[140] As early, rather than late, PTD is associated with infection, maternal plasma G-CSF may be a useful marker to identify women with infection-related PTL.

Activation of the cytokine network increases protease production, which plays a role in the degrading of the fetal membranes as well as the cervical extracellular matrix (ECM).[79] Chorionic and cervical cells activated by IL-1 release collagenases[79] and IL-1 also induces stomelysin (MMP-3) expression.[141] Stromelysin degrades collagen, laminin and fibronectin and activates interstitial collagenase (MMP-1) as well, which degrades the fibrillar collagen matrix of the cervix.[141] In addition to protease expression, IL-1 enhances expression of IL-8 in amniotic, chorionic, decidual and cervical cells[142], which in turn, acts synergistically with PGE_2 to augment the release of metalloproteinases. Elevated amniotic fluid levels of IL-8 have been associated with PTD in women with intrauterine infection[79] and uterine IL-8 levels strongly correlate with MMP-8 and MMP-9 concentrations.[143]

Potential markers of infection have been studied in amniotic fluid, maternal serum and cervicovaginal fluid, but the clinical utility of measuring the concentrations of inflammatory cytokines in amniotic fluid is limited in clinical practice, because of the invasive method, which may accelerate delivery in women with PTL.[134] Women in labour (term or preterm) have significantly higher concentrations of serum IL-6, compared to women who are not in labour, and even higher concentrations are found in those women with infection-related PTL.[144] Lockwood *et al*. found that an increase in the concentration of IL-6 in the cervicovaginal fluid in asymptomatic women predicted spontaneous PTD with a sensitivity of 50%, a specificity of 85% and positive and negative predictive values of 47 and 86%, respectively.[138] However, they found no significant difference in the IL-6 concentrations of symptomatic women who delivered preterm compared to those who delivered at term, and concluded that cervical IL-6 levels were a relatively insensitive screening tool for PTD.

Inhibition of MMP's is achieved by an endogenous inhibitor, known as tissue inhibitor of metalloproteinases (TIMP's).[134] Maternal plasma MMP-9 levels increase three-fold with the onset of spontaneous labour, term or preterm, but whether MMP concentrations are useful to clinically predict PTD, remains to be determined by further clinical studies.[145]

Fetal fibronectin (fFN) in the cervicovaginal fluid may indicate disruption of the decidual-chorionic interface, resulting in the release of ECM components.[134] Goldenberg *et al*. found fFN to be a good predictor of PTD in symptomatic and asymptomatic women as well as a strong association between fFN levels and subsequent chorioamnionitis and sepsis.[128] In a small study to test the clinical potential of fFN, Gebhardt and Odendaal measured the levels of fFN in 11 women with preterm contractions and found that, in the five women who were negative, false labour was eventually diagnosed and four of them delivered after 36 weeks. The other six women had positive results and were being suppressed for actual PTL (contractions associated with cervical dilatation).[146]

2.4.1 Treatment of bacterial vaginosis in pregnancy

A number of critical questions regarding the management of infection, and in particular BV, during pregnancy remain unresolved. For example, should all pregnant women be screened for BV and treated if they are positive? Or, in which sub-populations of pregnant women will screening and treatment be beneficial? What grade of BV merits treatment, which antibiotic is the best and through which route of administration will the optimal cure-rate be achieved?

As previously mentioned, many clinical trials have been conducted to challenge the hypothesis that treatment of BV in pregnancy will reduce the rate of PTD, but because of the conflicting results, no "golden standard" of reference could yet be concluded. Oral therapy has been recommended as the treatment of choice

during pregnancy, as intravaginal medication is not effective against micro-organisms in the uterine cavity.[147] The oral treatment of choice would probably be metronidazole, which can be given as a single 2g dose, 2g daily for two days or 500mg twice daily for five to seven days.[148] In terms of compliance, a single 2g dose would be the treatment of choice, but a seven-day course has a better cure rate.[149] Clindamycin is also effective against *M. hominis*, but is much more expensive than metronidazole[150] and the cure rate for BV with erythromycin has been found to be significantly lower than with metronidazole ($p < 0.001$).[151] Erythromycin is also not effective against the hominis-species of the mycoplasmas.[152]

The most consistent finding from these studies is that oral treatment, early in pregnancy (< 20 weeks), reduces the risk of PTD in women *at risk* for PTD, with the risk factor being a prior history of PTD.[72,124,153] A possible explanation for this reduction is that in 40 – 50% of the woman recruited, the prior preterm deliveries may have been infection-related and with early treatment in the subsequent pregnancies, the recurrence risk was reduced.

Bacterial vaginosis has also been associated with endometritis[154] and first trimester miscarriage[105], lending support to the suggestion of early, rather than late, treatment of the condition. Furthermore, women who are BV positive already at 20 weeks' gestation are at higher risk for PTD than those who acquire the infection later.[121]

It does make sense to screen and treat all pregnant women as soon as possible after conception, especially those at risk for PTL, but there is little evidence that low-risk pregnant women who are BV positive will benefit from antibiotic therapy.[126,155]

2.5 PLACENTAL ABRUPTION

Placental abruption is defined as a premature separation of the placenta from the implantation site in the uterus prior to delivery and is preceded by a cascade of pathophysiologic processes.[156,157,158] It has been described as an uncommon, but serious complication of pregnancy.[159] The prevalence of placental abruption varies from 0.59% to 1.6%.[160,161] Data from the US as well as Norway, indicate that the incidence of abruption may be increasing.[162,163] Recorded abruptions in the US increased with 29% from 1979 to 1987 (8.2 – 11.5 per 1 000 births) and with 31% in Norway, from 1987 to 1991 (5.7 – 8.3 per 1 000 births).

Various etiological factors have been implicated, but in about 40% of the cases, no cause can be identified.[164] Placental abruption is a major cause of third trimester haemorrhage and is believed to be responsible for up to 25% of perinatal deaths.[159] This is due, at least in part, to the high rates of prematurity, growth restriction, and intra-uterine death that accompany abruption. Placental abruption has been associated with more than 60% of cases of premature labour.[164]

Placental abruption may involve one of two processes:[156]

1. Haemorrhage into the decidua basalis, resulting in a decidual haematoma and compromising placental function. The haematoma may be small and limited or may continue to dissect through the decidual layers.[157]
2. Rupture of the spiral arteries with a retroplacental haematoma, which expands rapidly, causing more vessels to rupture. Acute abruption results with extensive separation of the placenta.

The decidua is very rich in tissue factor, which is the primary initiator of haemostasis.[165] Following haemorrhage from the spiral arteries, membrane-

bound tissue factor from the decidual cells forms a complex with activated factor VII to activate factor Xa that, in turn, converts prothrombin to thrombin.[165] Thrombin promotes the generation of fibrin, activation of clotting factors VII and V and platelet activation to produce a retroplacental or retromembranous clot.[79] In addition, thrombin also enhances the production of tissue-type and urokinase-type plasminogen activators (tPA and uPA) that break down the fetal membranes and decidua.[166] The PA's exert their primary effect on ECM degradation by generating plasmin, which can degrade laminin, collagen III and fibronectin and activate MMP's.[79] Thrombin also binds to myometrial receptors, resulting in the stimulation of uterine contractions.[167]

The precise cause of abruptio placentae is still largely unknown, but most explanations center around vascular or placental abnormalities, including abnormal placentation.[168] It is likely that in some cases, the underlying cause of the abruption occurs very early in gestation. In normal pregnancy, the uterine spiral arteries undergo transformation from muscular arterioles to low-resistance, dilated vessels. Such changes occur as a result of trophoblastic invasion during both the first (10 – 16 weeks) and second (16 – 20 weeks) trimesters. The lack of trophoblastic invasion of uterine vessels results in decreased placental blood flow and dysfunctional endothelial responses to vasoactive substances.[157] These abnormal placental vessels may predispose to ischaemia and rupture of the vessels involved, thus causing placental abruption.[169] The absence of these normal changes is found in pregnancies complicated by hypertensive disorders, explaining the risk of fetal asphyxia in these pregnancies.[157]

The highest incidences of abruptio placentae are reported among women with hypertensive diseases, with severe pre-eclampsia yielding a relative risk of 3.8 (95% CI 2.1 – 6.9) to 5.12 (95% CI 3.1 – 8.46).[161,168] The relative risk for women with chronic hypertension is slightly lower at 2.76 (95% CI 1.1 – 4.18).[161]

Preterm labour, low birthweight and stillbirths (antepartum and intrapartum) have also been strongly associated with abruptio placentae. In a recent retrospective, cohort study by Anath *et al.*, they reported a 1% prevalence of placental abruption among 53371 singleton pregnancies.[158] The frequency of PTD among women with abruption in this cohort was 39.6%, resulting in a 6.6-fold (95% CI 5.4 – 7.9) increase in relative risk after adjusting for confounding factors, including hypertensive disorders. The adjusted relative risks for LBW and stillbirths were 4.6 (95% CI 4.0 – 5.3) and 8.9 (95% CI 6.0 – 13.0), respectively. A possible explanation for the association of idiopathic PTD with abruption is the extravasation of blood at the placental margin, leading to decidual necrosis, which, in turn, could initiate prostaglandin production and thus lead to PTL.[170]

The risk for placental abruption is especially high among smokers.[157,171] In a Swedish study, the odds ratio for perinatal death from placental abruption in smokers compared to non-smokers was 1.4 (1.1 – 1.8) for those women who smoked one to nine cigarettes per day and 1.7 (1.2 – 2.2) for those who smoked 10 or more per day.[172] A similar association was found in the United States where the adjusted relative risk for placental abruption among smokers compared to non-smokers was 1.65 (1.44 – 1.91) for those smoking one to 10 per day and 1.73 (1.45 – 2.01) for those women smoking more than 10 per day.[173]

In a large retrospective cohort study, Anath *et al.* found that smoking, together with any hypertensive disorder, result in an even higher risk for abruptio placentae.[168] The increase in adjusted relative risk for the different hypertensive disorders among smokers is shown in Table 2.3. In the population studied, 1107 pregnancies (0.97%) were complicated by placental abruption among a total of 120666 singleton pregnancies.

Table 2.3 Joint effect of smoking and hypertensive disorders on the risk of placental abruption.

Smoking	Hypertensive disorder	Abruption (%)	Adjusted Relative Risk	95% CI
No	None	0.68	1.0	
	Chronic HPT	0.55	0.7	9.2-2.9
	PE (mild)	0.61	0.9	0.6-1.2
	PE (severe)	2.96	4.1	2.8-6.0
	Chronic HPT + PE	1.52	2.0	0.7-5.4
Yes	None	1.44	2.1	1.8-2.4
	Chronic HPT	4.55	4.6	1.7-12.7
	PE (mild)	1.66	2.3	1.6-3.3
	PE (severe)	4.49	5.9	3.4-10.3
	Chronic HPT + PE	6.12	7.8	2.4-25.9

PE = pre-eclampsia, HPT = hypertension

Modified from Anath *et al.* [168]

Other risk factors for abruptio placentae include:

- maternal abdominal trauma[174]
- hereditary coagulopathies[79]
- intra-uterine growth restriction[156]
- coitus in late pregnancy[156]
- rapid decompression of the uterus[171]
- folate deficiency[175]

2.6 PATHOLOGIC UTERINE DISTENTION

Uterine distention is a critical component of the mechanisms that regulate CAP expression during normal parturition.[1] Conditions that are associated with pathologic uterine distention are those that promote an abnormal increase in uterine volume, e.g. multiple pregnancies or polyhydramnios, or those that limit uterine expansile capacity, such as a T-shaped uterus or Müllerian-duct anomalies.[79] In both of these clinical conditions, the rate of increase in intrauterine volume seems to exceed the ability of the uterus to cope. Also, both conditions have been strongly associated with PTL and PPROM.[79] The mechanism that may be responsible for this association involves a signal, initiated by the physical stretch of the myometrial, fetal membrane and cervical cells, which activates cellular protein kinases.[79]

Acute stretching of myometrial cells leads to increased expression of myometrial gap junctions[11] and increased MLCK activity.[79] Mechanical stretch of the fetal membranes is similarly associated with increased IL-8 and collagenase expression.[176] Early *in vitro* studies demonstrated that mechanical stretching of amniotic, cervical and myometrial cells result in the synthesis of prostaglandins E_2 and $F_{2\alpha}$.[79] These effects have been used clinically in the form of inflatable catheters to induce cervical ripening and labour.[177]

2.7 CONCLUSION

Although each of the pathogenic mechanisms described has distinct clinical and biochemical characteristics, they all converge on a final common pathway, i.e. uterine contractions and subsequent preterm delivery.[79] From these results came the hope that some of the biological markers associated with the specific pathways involved, may be useful predictors of PTD.[165] However, some of these

proposed markers have proved disappointing. Leung *et al.* found maternal serum CRH levels higher than 1.9 multiples of the median, to positively predict only 3.6% of women who will deliver before 34 weeks.[106] Elevated levels of maternal salivary estriol, a proposed marker of early activation of the fetal HPA-axis, have also been found to have a low positive predictive value for PTD.[178]

Markers associated with the final common pathways of prematurity - uterine contractions and the disruption of the ECM within the cervix and fetal membranes - have also been proposed as another approach to predict PTD.[165] Home monitoring of uterine activity, cervical length measurement and fFN in cervicovaginal fluid have been found to have low individual positive predictive value for PTD before 35 weeks in asymptomatic women.[179] However, the high negative predictive values of these factors may be valuable in the sense that women who will not need intervention later may be identified and followed up as low-risk patients. Combining markers may improve the ability to predict PTD.

The Preterm Prediction Study Group evaluated 28 potential biological markers for spontaneous PTD in asymptomatic women at 23 to 24 weeks gestational age. With the use of only the three serum tests as a group (alkaline phosphatase, α-fetoprotein and granulocyte colony-stimulating factor), any positive test identified 80.5% of women who delivered preterm (OR 14.7; 95% CI 5.0 – 42.7), with a specificity of 78.1%.[180] However, the overlap between the strongest biological markers for PTD is small. This once again confirms there are several pathways that may lead to PTD and suggests that several biological markers together may be useful in the creation of a multiple-marker test with high sensitivity and odds ratio.[180]

To date, the tocolytic agents used to stop uterine contractions once PTL has started, has not been able to reduce PTD with clinical significance.[74] Long-term tocolysis has not been shown to prolong pregnancy or improve neonatal

outcome[165], although some agents may delay delivery long enough for the administration of antenatal corticosteroids and transfer to a tertiary care unit.[74]

Antibiotics are prescribed routinely to pregnant women presenting with spontaneous preterm labour, but to date there has been no proof of any real benefit as studies have shown a mixed pattern of results. The ORACLE Trial was undertaken in order to resolve some of these uncertainties, one of them being prolonging pregnancies threatened by PTL with the prescription of antibiotics.[111] A total of 6295 women in spontaneous PTL before 37 weeks and without any clinical signs of infection were randomised to receive on of four possible treatments: 325mg co-amoxiclav (250mg amoxicillin and 125mg clavulanic acid) plus 250g erythromycin; co-amoxiclav plus erythromycin placebo; erythromycin plus co-amoxiclav placebo; or co-amoxiclav placebo plus erythromycin placebo. Of these women, 6241 completed the trial. There was no evidence that use of any antibiotic regimen prolonged pregnancy, influenced the mode of delivery or the length of hospital stay. Most of the women did not deliver within 48 hours (89.9%) or within seven days of admission (84.6%), which illustrates the difficulty in predicting which women in PTL will eventually deliver preterm. The conclusion from this study was that neither β-lactam nor macrolide antibiotics prolong pregnancy or improve neonatal health when prescribed for women in spontaneous PTL without clinical infection.[111] A possible explanation for these results is that the timing of the administration of antibiotics was too late (clinical signs and symptoms of labour were already established) in order for them to have any beneficial effect. A second possibility is that the role of subclinical infection as a cause of PTL has been overestimated and should be reassessed in different populations.[111] Antibiotics should therefore not be routinely prescribed for women in acute PTL without any signs of clinical infection.[111]

The second leg of the ORACLE Trial challenged the hypothesis that babies of women in PTL with rupture of the fetal membranes will benefit from antenatal antibiotic therapy, i.e. reducing the prevalence of necrotising enterocolitis (NEC), major cerebral abnormality, respiratory distress syndrome and intra-uterine or neonatal death.[181] Women were eligible if they were less than 37 weeks pregnant, if PPROM was present and if the need to prescribe antibiotics were uncertain (these criteria most likely reflected clinical practice). A total of 4826 women were randomised to receive one of the four combinations of antibiotics as for the first leg of the trial (see above) and 4809 completed the trial. In the erythromycin plus co-amoxiclav group and in the two groups assigned any antibiotic, significantly fewer women delivered within 48 hours than those on placebo. Results were similar for delivery within seven days.[181] The prescription of erythromycin resulted in the reduction of neonatal treatment with surfactant, reduction in positive neonatal blood cultures, reduction in chronic lung disease (neonatal ventilation or oxygen at > 28 days), reduction in the rate of major cerebral abnormality and reduction in the composite primary outcome of death. Erythromycin was less effective than co-amoxiclav in prolonging pregnancy and reducing maternal infection, but proved to be more effective against neonatal disease with less evidence of harm. In contrast, co-amoxiclav was associated with a significant increase in the prevalence of neonatal NEC. This finding was also present, although to a lesser extent, in the first leg of the trial.[181] The result of this trial show that a cheap and widely available antibiotic, erythromycin, when given to women with PPROM, reduces the occurrence of neonatal disease and may therefore have a substantial health benefit on the long-term respiratory and neurological function of many children.

"Our limited ability to stop preterm labour once it has started is even more disheartening than our frustrated efforts to predict it."

This comment by Dr Charles Lockwood may summarise the general sentiment about preterm labour and delivery among health care workers and researchers.[165] The multifactorial etiology of preterm labour is of course what makes it so difficult to predict and once PTL has begun, the damage has already been done, so to speak. It may be helpful to determine the possible risk factors unique to a given population and not generalise findings from studies conducted among women form different ethnicity, socioeconomic status and even a different country.

The ideal would of course be early intervention in women at risk for PTL, but until such biological markers or prophylactic agents other than antibiotics are available, we are still faced with a challenge that we cannot afford to give up on.

CHAPTER 3: VIOLENCE AGAINST WOMEN – IMPACT ON REPRODUCTIVE HEALTH

I Got Flowers Today

I got flowers today. It wasn't my birthday or any other special day.

We had our first argument last night, and he said a lot of cruel things that really hurt me.

I know he is sorry and didn't mean the things he said, because he sent me flowers today.

I got flowers today. It wasn't our anniversary or any other special day.

Last night he threw me into a wall and started to choke me.

It seemed like a nightmare. I couldn't believe it was real. I woke up this morning sore and bruised all over.

I know he must be sorry because he sent me flowers today and it wasn't Mother's Day or any other special day.

Last night he beat me up again. And it was much worse than all the other times. If I leave him, what will I do? How will I take care of my kids? What about money? I'm afraid of him and scared to leave.

But I know he must be sorry. Because he sent me flowers today.

I got flowers today. Today was a very special day. It was the day of my funeral.

Last night he finally killed me. He beat me to death.

If only I had gathered enough courage and strength to leave him, I would not have gotten flowers today.

- Author unknown

3.1 INTRODUCTION

Around the world at least one in every three women has been beaten, coerced into sex, or otherwise abused in her lifetime. Most often the abuser is a member of her own family. Increasingly, gender-based violence is recognised as a major public health concern and a violation of human rights.

The effects of violence can be devastating to a woman's reproductive health as well as to other aspects of her physical and mental wellbeing. In addition to causing injury, violence increases a woman's long-term risk of a number of other health problems, including chronic pain, physical injury, disability and even death. In order to deal with their situations, women turn to alcohol and drugs or may fall into the claws of depression, sometimes leading to suicide. Women with a history of abuse are also at increased risk for unintended pregnancy, sexually transmitted infections and adverse pregnancy outcomes.

During pregnancy, there are two lives being affected in a violent relationship. The baby is at risk of being born prematurely, suffer from severe morbidity and even die. Should the child survive, there is the chance of being neglected by a depressed mother who may not have wanted the baby in the first place, Maybe she was unable to negotiate contraceptive use or was forced into having sex when she didn't want to. The child may also be subjected to violence or may witness the mother being abused, increasing the risk of the child to grow up thinking that violence is the norm, and become an abusive partner or end up in an abusive relationship.

3.1.1 What is violence against women?

In 1993, the United Nations offered the first official definition of such violence when the General Assembly adopted the Declaration on the Elimination of Violence Against Women. According to Article 1 of the declaration, violence against women include: "any act of gender-based violence that results in, or is likely to result in, physical, sexual or psychological harm or suffering to women, including threats of such acts, coercion or arbitrary deprivations of liberty, whether occurring in public or private life."[182] Violence against women is often referred to as "gender-based violence", because at the heart of it, is the inequality of the genders. Many cultures have beliefs, norms and social institutions that legitimize and therefore perpetuate violence against women. The same acts that would be punished if directed at an employer, a neighbour or an acquaintance would often go by unnoticed when men direct them at women, especially within the family.

Two of the most common forms of violence are abuse by intimate male partners and coerced sex, whether it takes place in childhood, adolescence or adulthood.

3.1.2 Magnitude of the problem

Intimate partner abuse, also referred to as domestic violence, wife-beating and battering, is almost always accompanied by psychological abuse and in 25 - 50% of cases, by forced sex as well.[183] In León, Nicaragua, among 188 women who were physically abused by their partners, only five did not experience sexual and/or psychological abuse as well.[184] Another study in the same area, found the lifetime prevalence of intimate partner violence among 360 women who were ever married or in a common-law relationship, to be 52% and 8% among 79 women who never lived with a partner, but only dated.[185] Among the ever-married women, 27% reported abuse during the previous year. In a cross-sectional study in three South African provinces, Jewkes *et al.* reported the prevalence of ever experiencing physical abuse

among 1 306 women to be 26.8% (Eastern Cape), 28.4% (Mpumalanga) and 19.1% (Northern Province), respectively.[186] The prevalence of rape was 4.5%, 7.2% and 4.8% and the prevalence or physical abuse during a pregnancy was 9.1%, 6.7% and 4.7%, respectively.

The majority of women who are abused by their partners experience repeated episodes of violence.[183,187] In the León study, for example, 60% of the women were abused more than once in the previous year and 20% of them experienced severe violence more than six times during the same period.[185] McCauley *et al.* reported that 39% of the women in their survey reported two to three episodes of abuse during the previous year and 27.3% were abused more than four times.[188] Sometimes overlooked, is the atmosphere of terror that often dominates such relationships. Women often say that the fear, psychological abuse and degradation are even more difficult to bear than the physical abuse.[183]

....He used to tell me, "You're an animal, an idiot, you are worthless." That made me feel even more stupid. I couldn't even raise my head...[184]

Women are threatened by many different types of violence throughout their lives; from a fetus *in utero* to old age (Figure 3.1).[189]

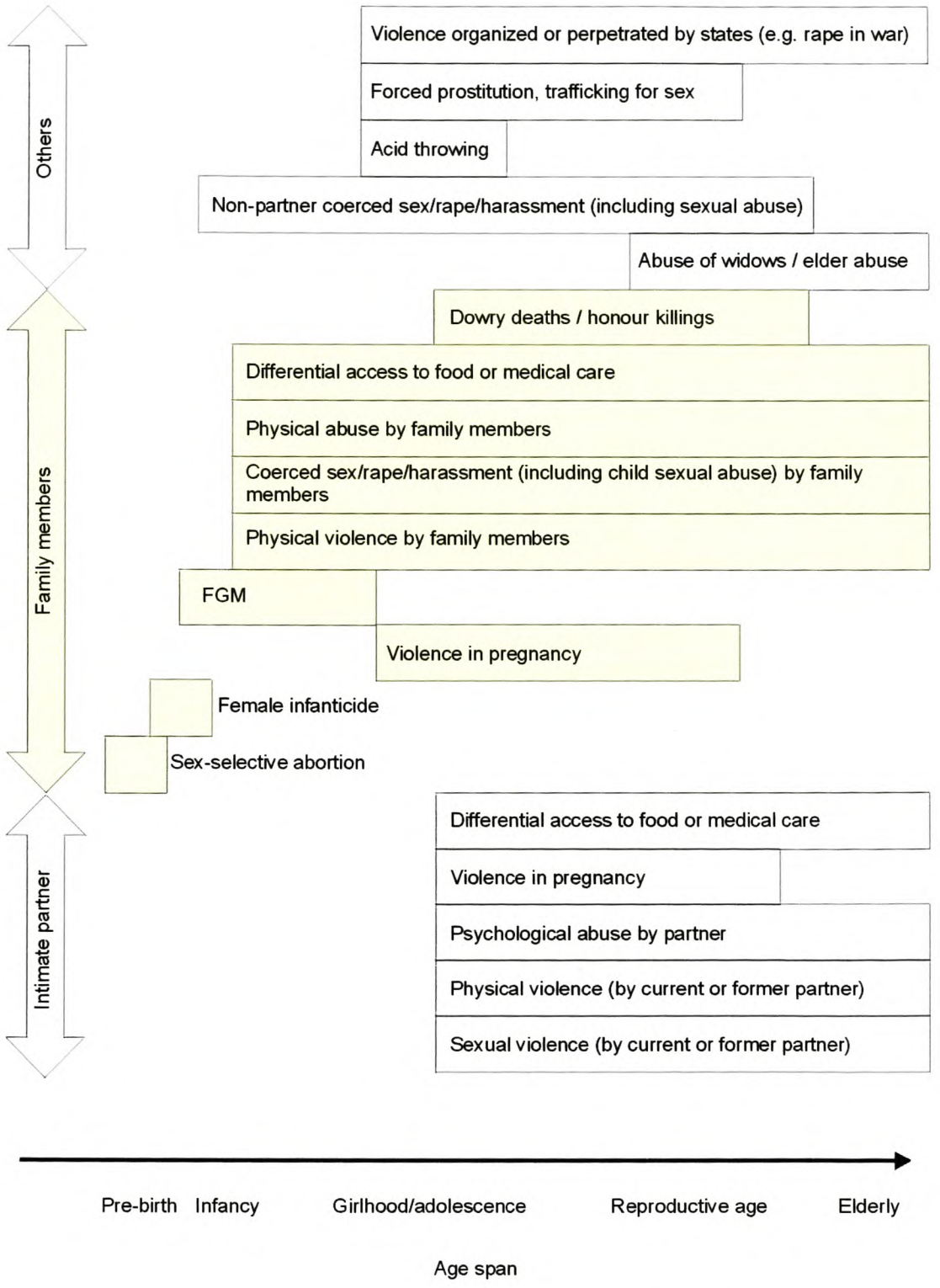

Figure 3.1 Violence and abuse against women over time. From Watts *et al.*[189]
FGM = female genital mutilation

3.1.3 Explaining intimate partner violence

Unlike many other health problems, there are few social and demographic characteristics that define risk groups for intimate partner violence.[190] Increasingly, researchers are using an "ecological framework" to understand the interplay of personal, situational and cultural factors that combine to cause abuse (Figure 3.2).[183] The model can be visualised as four concentric circles.

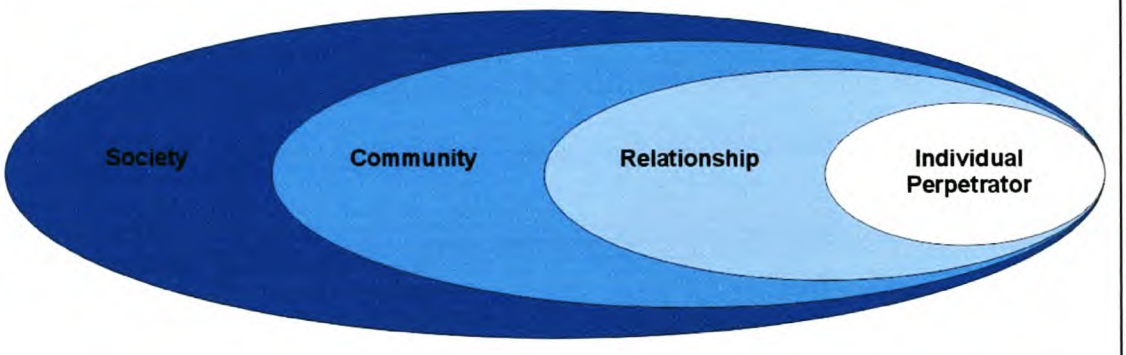

Figure 3.2 Ecological factors associated with partner abuse. From Heise *et al.*[183]

- The inner circle represents the biological and personal history that each individual brings to his or her relationships, manifesting through behaviour. Some factors that will increase the likelihood of a man abusing his partner include being abused as a child or witnessing marital violence growing up, having an absent or rejecting father and frequent alcohol use.
- The second circle represents the immediate context in which abuse takes place, in this case the intimate relationship. Marital conflict and male authority (economic and decision-making) in the family are strong predictors of intimate partner abuse. Female empowerment, especially educational attainment, seems to be protective against abuse.[190]
- Household authority is largely determined by social structures, which is represented by the third circle. This contains the world of extended family, the workplace, neighbourhood and social networks. Isolation of

women and lack of social support, together with male peers that condone violence, predict higher rates of violence.

- Finally, the outer circle includes the dominant cultural views and attitudes of that permeate the society at large. Violence appears to be more prevalent in societies where gender roles are rigidly defined and enforced, and where the concept of masculinity is linked to "toughness", male honour or dominance. Other cultural norms that have been associated with gender-based violence include the perception that men have "ownership" over women and the use of violence as a means to settle interpersonal disputes.[183]

3.1.4 Cycle of violence

...After he beat me up, he would always come back to court me, bought me clothes and afterwards he always said, "Forgive me, I won't do it again." But then he always did the same afterwards. And then my grandmother would say to me, "Child, what are you going to do with candies in hell?"

Ana Cristina, Nicaragua[184]

Domestic violence crosses all racial, ethnic, religious, educational and socioeconomic lines.[191] That violence only occurs in "problem" or "low-class" families is a myth – it also occurs among highly educated, seemingly well-adjusted couples.[187,192,193] Unfortunately, the incidence of domestic abuse among the middle- and upper-income families is not really known, because these families tend to hide the abuse very well, because of the shame and myths about battering.[193,194] Family violence has been found to be a progressive phenomenon that tends to occur in a predictable cycle (Figure 3.3).[191] A three-phase cyclic pattern of the battering behaviour has been described. It begins with a period of increasing tension that gradually escalates, leading to the battering, which is then followed by a period of calm and remorse where the perpetrator displays kind, loving behaviour and pleads for forgiveness. The "honeymoon phase" usually restores the hope in the

woman that the man will change and is the reinforcement for remaining in the relationship. It also causes the woman to deny the inevitable recurrence of the abuse.[194]

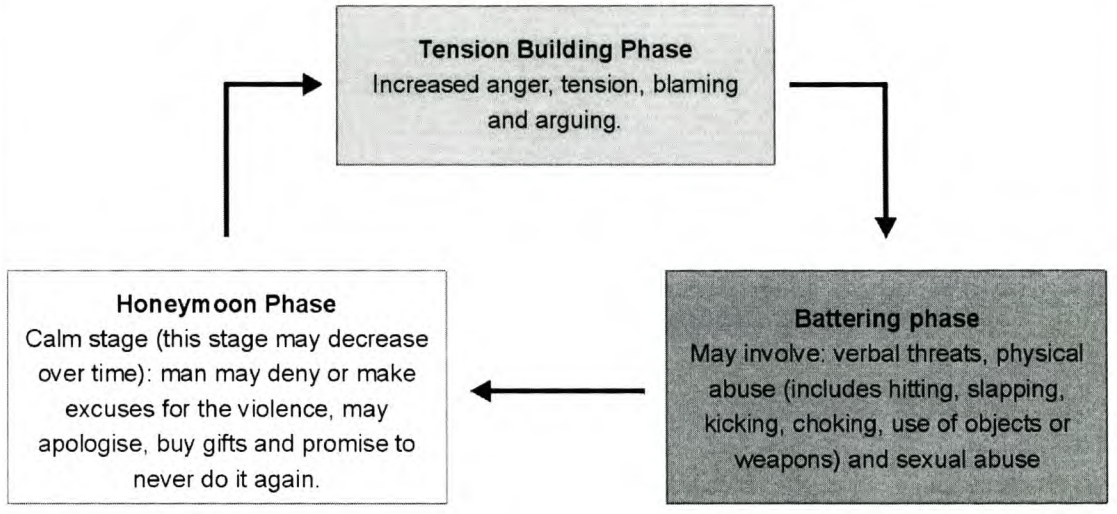

Figure 3.3 Cycle of domestic violence. Source: Rynerson[194]

3.1.5 Sexual coercion

Sexual coercion can range from forcible rape to nonphysical forms of pressure that will compel girls and women to have sex against their will. The touchstone of coercion is that a woman lacks choice and can face severe physical or social consequences if she resists sexual advances.[183] Some forms of coercion, including forced penetration (rape), sexual assault (forced sexual contact) and sexual molestation of children, are recognised as crimes by many legal systems. Other forms of coercion, such as intimidation, verbal abuse, or forced marriage, are tolerated and even condoned in some cultures. Still, other forms may involve organized crime or the military, for example trafficking in women and rape in war.[182,183] Although the common image of a rape is a violent attack by a stranger, in reality, most forced sex is perpetrated by someone known to the victim.[189]

Sexual coercion can take place at any point in a woman's life. We need only to read the newspapers in South Africa to know that babies, only a few months old, are being raped. Also women of older age are not excluded, e.g. in a Swedish report, women of 60 years old were found to be battered and sexually abused by their husbands.[193]

3.1.6 Forced sex in marriage

The most nonconsensual sex takes place among people who know each other[182,193] and sadly much of that happens within the union of marriage. Many women, however, do not consider forced sex as rape if they are married to, or living with, the perpetrator. Although some countries have now recognized marital rape as a criminal offence, others still argue that husbands have legal rights to unlimited sexual access to their wives.[182] In a descriptive study, 36% of abused women reported that they were often forced to have sex while being beaten.[184]

3.1.7 Forced sexual initiation

For a minority of women, sexual initiation is a traumatic occurrence, accompanied by force and fear. Although sexual initiation is not always physically forced, it is nonetheless unwanted and experienced as something that happened to them, rather than something they chose and remember as a special event.[185.196] In the words of a teenage girl, "...there has to be something good about it for people to like it so much – maybe it's just me who hasn't found it".[196]

In a study among adolescents in the Eastern Cape, 28% of the girls reported that they were forced into having sex for the first time by their partners. In the same study, 20% gave peer pressure as the reason for initiating sexual activities.[197] Research also suggests that the younger a woman is at her first sexual experience, the more likely it is that force was used.[189] A national study of 458 women in New Zealand, found that 25% of women who had

intercourse before the age of 14 were forced to do so, often by a much older man.[195] Adolescent boys have admitted that coercion, including drugging and gagging, of female partners is common.[183]

3.1.8 Sexual abuse in childhood

Childhood is supposed to be a time of carefree exploration, growth and support. For many girls (and boys) the reality is quite different. Child sexual abuse refers to any sexual act that occurs between an adult or immediate family member and a child and, any nonconsensual sexual contact between a child and a peer.[183] Sexual abuse does not always involve sexual intercourse and physical force, but is usually characterised by deception and coercion.[198] Childhood sexual abuse is often a chronic violation, rather than a one-time incident. It is reported that the vast majority of perpetrators are male and known to the victim.[183] Epidemiological reports estimate that almost as many as one in every four women have been sexually abused as children.[198] In an anonymous survey, 22% of 1931 women reported childhood sexual or physical abuse.[199] Another cross sectional survey, involving 1193 adolescents aged 13 – 17 years, reported that 33.8% of girls and 10% of boys (total = 21%) had experienced at least one sexually abusive event.[200] The prevalence of abuse involving physical contact was 20.4% among girls and 3.3% among boys. Sexual abuse involving some form of penetration was reported by 5.6% of the girls and 1.1% of the boys.[200]

The trauma associated with childhood sexual abuse, and incest in particular, has the potential to be among the most devastating experiences that can be endured. It is therefore not surprising that there is a strong association between sexual abuse and a variety of short- and long-term adverse physical and psychological consequences.[198]

3.2 IMPACT OF VIOLENCE ON WOMEN'S REPRODUCTIVE HEALTH

Physical and sexual abuse lies behind some of the most serious reproductive health issues of our time – unwanted pregnancies, HIV and other sexually transmitted infections (STI's) and pregnancy complications. Violence operates through multiple pathways to affect women's sexual and reproductive health (Figure 3.4).[183] Physical and sexual abuse can directly put a woman at risk for infection and unwanted pregnancy, if she is forced to have sex or is unable to negotiate condom use out of fear of her partner's reaction.

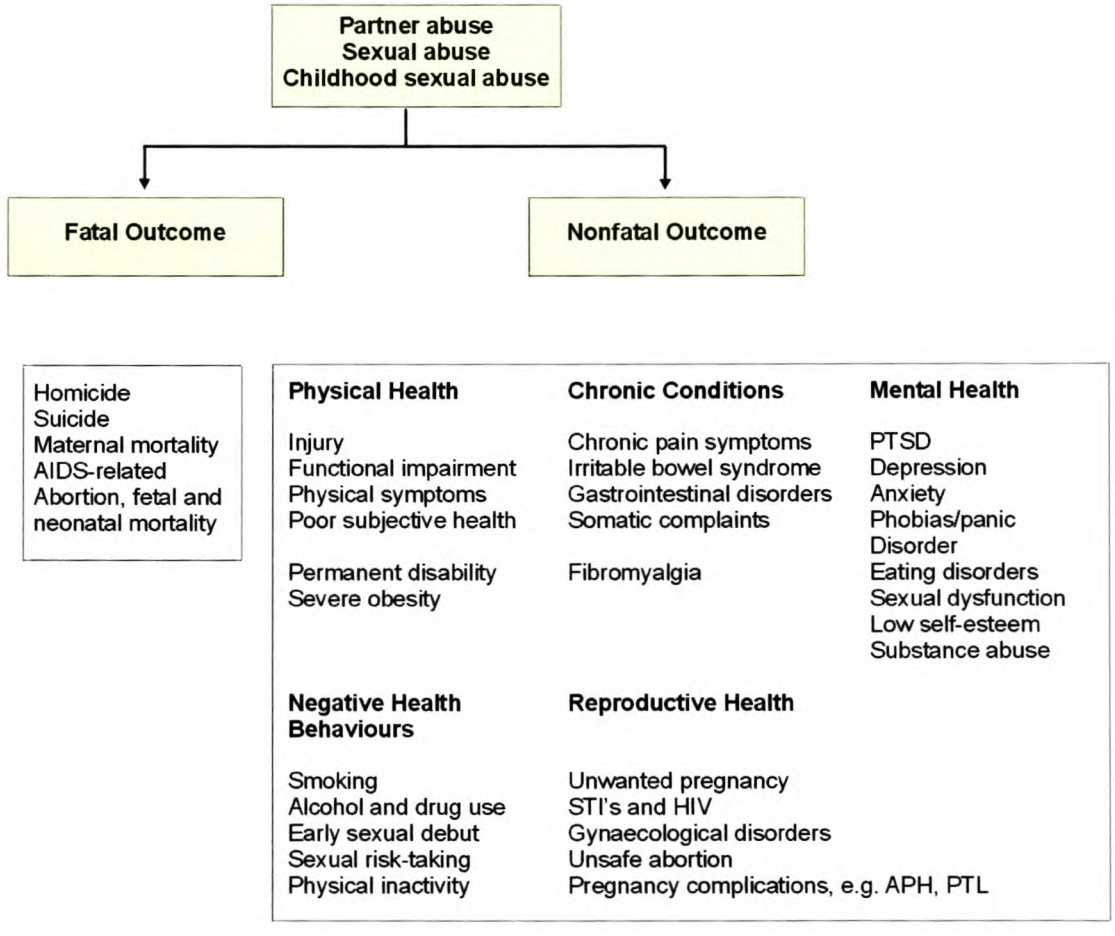

Figure 3.4 Health outcomes of violence against women. Adapted from Heise *et al.*[183]

Childhood sexual abuse can indirectly lead to unwanted pregnancies or STI's through high-risk sexual behaviour in adolescents and adults.

3.2.1 UNWANTED PREGNANCY

In many parts of the world, marriage is interpreted as granting men the right to unconditional sexual access to their wives and the power to use force if necessary.[183] Women who lack sexual autonomy are often powerless to refuse unwanted sex or to use contraception and are therefore at risk for unwanted pregnancies. In a survey among pregnant teenagers in Khayelitsha (an informal township near Cape Town), 71% said that they were forced to have sex and 75% admitted that fear of being beaten up kept them from refusing sex.[196]

It has been assumed that having many children may increase a woman's risk of being abused, for example by increasing marital disagreements or stress. However, results from a study in Nicaragua, suggests that domestic violence increases the likelihood that a woman will have many children.[184] The study found that abused women were twice as likely than other women to have four or more children. The association between physical violence and sexual coercion as well as control of the man over contraception use found in this study, lends support to this interpretation. Focus group discussions revealed that some men deliberately kept their wives pregnant, the excuse being, to reduce the likelihood of their being unfaithful. A common saying in Nicaragua is: "women should be kept like a farm shotgun – always loaded."[184] Therefore, in some populations, violence can be a risk factor for having many children, rather than a consequence.

3.2.1.1 Contraceptive use

Many women are afraid to raise the issue of contraceptive use for fear that their partners may respond violently.[201,202,203] In some cultures men react negatively and even violently, as they believe that contraceptive use will

encourage their wives to be unfaithful.[183] Where having many children is a sign of a man's virility, a man may interpret his wife's wish to use contraception as an insult to his masculinity.[203] A strong influence on whether a woman will use contraception or not, is how she perceives her partner's attitude towards family planning.[202] Across 13 surveys, an average of 9% of married women who wanted to avoid pregnancy, but was not using contraceptives, gave the disapproval of their husbands as the principal reason for not doing so.[201] It has been suggested that these couples represent a large share of couples with an unmet need for family planning (wanting to avoid pregnancy, but not using any form of contraception).[204]

Women often use contraception secretly out of fear of being beaten or abandoned if they would do so openly. In Cape Town, young women described how their partners beat them and tore up their appointment cards for the Family Planning Clinic.[205]

Fortunately, there are studies suggesting that men are more open to family planning than their wives or partners may think.[206] Communication about sex within a marriage or relationship is often so limited that women often do not know their partner's view of family planning. These women may just assume that their partners' attitude towards contraception mirrors the disapproving cultural norms, when in fact they may approve.[183]

3.2.2 HIGH-RISK SEXUAL BEHAVIOUR

3.2.2.1 Adolescent pregnancies

Adult survivors of childhood sexual abuse can suffer from a number of psychological and behavioural problems.[198] Of the psychological problems include post-traumatic stress disorder (PTSD), chronic depression, anxiety, low self-esteem, suicidal thoughts, alcohol and substance abuse and eating disorders.[199,207] These girls are also more likely to have an early voluntary

sexual debut, multiple sexual partners and to not use contraception.[208,209] This type of behaviour puts them at high risk for unwanted pregnancies and STI's. Risky sexual behaviour may be an effort of these girls to gain control of a childhood experience in which they felt powerless and violated.[183] To victims of sexual abuse, sex may be the only "fatherly love and affection" that they knew when growing up, and that may then become the foundation on which they build future relationships with boys and men. This may be especially true where the perpetrator was a biological father or the father figure in the house.

Women who were sexually abused are more likely to become pregnant as teenagers. A US study found that victims of sexual abuse are almost three times more likely to become pregnant before the age of 18 than teenage girls who were not abused.[210] A pregnancy at this young age is almost always unplanned and very likely unwanted, which will cause many young women to solve the dilemma through termination of the pregnancy.[182] In countries where abortion is illegal, many may resort to illegal abortions, at times with fatal consequences.[182]

Unsafe abortion, defined as "a procedure for terminating an unwanted pregnancy either by persons lacking the necessary skills or in an environment lacking the minimal medical standards, or both", is almost non-existent in developed countries.[211] Where abortion is illegal, some providers still do safe abortion, and do so because they are genuinely sympathetic to the women's plight, but some practitioners exploit their clients.[212] High prices are very often charged and some women may even have to provide sexual services to male providers as part of the payment.[212] There is up to a 500-fold difference in the risk of death when an unsafe abortion is performed using traditional methods, rather than a first-trimester abortion using vacuum aspiration (Table 3.1).[213] Traditional methods include the use of sticks or roots, risking infection, haemorrhage, uterine perforation and damage to the posterior fornix.[212]

Table 3.1 Differences in risk of deaths from abortion in developed and developing countries.[213]	
Region	**Deaths per 100 000 abortions**
Developing countries (mainly unsafe)	330
Africa	680
South East and South Asia	283
Latin America	119
Developed countries (mainly safe)	0.2 – 1.2

Sex education and free and easy access to contraception have not helped to reduce the rates of teenage pregnancy.[183] Risk factors that were found to predispose a young child to abuse, such as absent or dysfunctional parents, were also associated with risk of adolescent pregnancy.[214] These findings lead researchers to question whether sexual abuse itself contributes to teenage pregnancy or whether both are caused by a third factor, such as disorganised, unhealthy home life.[214] Studies that examined the effects of sexual abuse, found that it has an independent effect on adult sexual behaviour and social functioning.[208,214,215]

Childhood abuse has also been linked to unintended pregnancies among adult women. In a study of 1193 women in the USA, 45% of the women reported that their first pregnancy was unintended.[216] Of these, 20% were associated with childhood abuse. The study also found a dose-response association between exposure to childhood abuse or household dysfunction and unintended first pregnancy in adult women.

In addition to abused girls being at higher risk of becoming pregnant as teenagers, boys who have been exposed to physical or sexual abuse or who witnessed their mothers being abused, are significantly more likely to be involved in a teenage pregnancy, both in adolescence and adulthood.[217]

3.2.2.2 Sexually transmitted infections, including HIV/AIDS

Childhood sexual abuse appears to increase the risk of STI's among adolescents largely through the association with high-risk sexual behaviour.[207,208] A recent report indicated that adults who were exposed to four or more of seven adverse childhood experiences (i.e. psychological, physical or sexual abuse; violence against mother; or living with household members who were substance abusers, mentally ill or suicidal, or imprisoned), were two to four times more likely to smoke, to have had 50 or more sexual partners and to have STI's.[207] They also had a four to 12-fold increased risk of alcoholism, depression, abuse of illicit drugs and suicide attempts.

Selling sex for money or drugs has also been linked to a history of childhood sexual abuse.[210] In Rhode Island, USA, it was found that men and women who had been raped or forced to have sex, either in childhood or adolescence, were four times more likely to work as prostitutes than people who were not abused.[210] They were also twice as likely to have multiple sexual partners in a single year and to engage in casual sex. Among the women, the victims of childhood abuse were twice as likely to be heavy consumers of alcohol. The abused women in this study did not have higher rates of HIV. Abused men, however, were twice as likely than those who were not abused to be HIV positive, independent of intravenous drug use or prostitution.[210]

Abuse in childhood also increased the risk of STI's through its effect on drug use. Many abused or assaulted women (and men) turn to drugs and alcohol as a coping mechanism. In order to feed their habit, they often engage in high-risk sexual behaviour such as unprotected sex and trading sex for money or drugs.[183]

Victims of other types of violence, such as intimate partner abuse, are also at risk of STI's. In the USA, women who reported abuse were more than twice

as likely than other women to have had a STI, even after controlling for confounding factors.[183] A possible explanation is that abusive men are more likely to engage in extramarital sex. In the words of one woman (who was treated for syphilis) at an antenatal clinic, "I know that I will get the infection again, because he won't wear a condom when he sleeps with other girls or with me" (personal experience).

3.2.3 VIOLENCE COMPROMISES PROTECTION AGAINST HIV

In a recent speech, Peter Piot, the Executive Director of UNAIDS, noted that violence against women has many links to HIV and AIDS. "Violence is not just a cause of the AIDS epidemic, it can also be a consequence of it".[218]

3.2.3.1 Condom negotiation

If a woman fears being beaten when she tries to negotiate the use of condoms, violence directly increases her risk for HIV-infection and other STI's.[183] For some women, condom use is even more difficult to discuss than other contraceptives, because of the stigma of promiscuity, infidelity and prostitution.[183] Raising the issue of condom use within a legal or common-law marriage is especially difficult for women. Bringing up condom use may implicate that one of the partners is unfaithful and that, in itself, is a big risk for a violent response.[219,220]

The notion that violence is an appropriate response when a woman requests the use of a condom was uniquely demonstrated among a group of migrant workers in South Africa. During an "anti-HIV" street play, the audience of about 1000 men broke into cheers when the male character hit his wife for suggesting that he use a condom.[183]

3.2.3.2 Voluntary counselling and testing

When women fear violent reactions from their partners they stay away from voluntary counselling and testing. This holds implications for both controlling sexual transmission of the disease and for efforts to reduce mother-to-child transmission (MTCT).

Researchers in Nairobi asked 243 HIV-infected women whether they have disclosed their HIV-status to their partners. Only 66 had done so. Of these women, at least 11 were chased away or replaced by another wife, seven reported being beaten by their partners and one woman committed suicide. This group revised their protocol and counselled women on the risks and benefits of disclosing test results to an intimate partner. The reports of violence dropped markedly over the next year, with no drop in the percentage of partners counselled.[221]

Fear of a violent response from their partners, is a serious concern for many women undergoing HIV-testing. Domestic violence should therefore be considered when formulating partner notification policies and in HIV counselling.[222] In the USA, a survey among 136 health care workers involved in HIV-related services, 24% reported that at least one woman reported physical violence after disclosing her HIV-status to her partner and 45% had women who feared such a reaction.[183]

3.2.3.3 Reducing perinatal transmission

Efforts to reduce MTCT of the HIV-virus have also been hampered in some ways through fear of violence. Pregnant women who fear being banished or beaten by their husbands, are more likely to refuse HIV-testing or do not return for the results.[183] Fear of violence has also interfered with women's willingness and ability to comply fully with a short-course regimen of antiretrovirals.[183] The reluctance of these women may be attributed to the fear of having to reveal their HIV-status to friends and family, which will

expose them to abuse. Women who were advised to bottle-feed their babies to avoid HIV transmission raised similar concerns. In societies where breastfeeding is the norm, women fear that using a bottle will brand them as HIV-positive, exposing them to isolation from the community or abuse.[183]

3.2.4 HIGH-RISK PREGNANCY

Profile of a battered fetus

"The baby was born at 29 weeks gestation to a mother who had been beaten by her partner a week before the delivery. Despite delivery without trauma, the infant's left arm, neck and shoulder were badly bruised; and the baby's left eye was swollen. On the second day of life, echoencephalography identified a massive intraventricular haemorrhage. The baby died a few hours later. At necropsy, the cranial contents burst forth when the skull was opened. A massive intraventricular bleed with subarachnoid extension and oedema and parenchymal softening was present. Two one-centimeter clots were prominent. Two small haematomas were found in the right liver and there was a subpleural haematoma in the lower left lung. The kidneys, trachea and oesophagus were hyperaemic. According to the mother, this was her third abusive relationship and her current partner had hit her abdomen playfully several times during the pregnancy. The beating preceding the delivery was the only time he had struck her in anger. Her membranes ruptured while they were waiting in line at a restaurant and he forced her to first eat the food that he had ordered before allowing her to seek medical care..."

(LANCET, 1981)[223]

Around the world, almost one out of every four pregnant women will suffer psychological, physical or sexual abuse, mostly at the hands of her partner. For some women, abuse will only start during pregnancy or it will escalate, with blows often directed at the abdominal area.[224]

In a large review of USA-based studies on the prevalence of violence during pregnancy, Gazmararian *et al.* noted a range of 0.9 – 20.1%.[225] In most of

these 13 studies reviewed, a range of 3.9 – 8.3% was reported. In Canada, physical violence was experienced among 5.7 – 6.6% of pregnant women.[226,227] The prevalence of such abuse in other countries are similar, e.g. at least 6.8% in South Africa[186], 7% in Switzerland[192], 11% in Sweden[228] and 13% in Nicaragua.[184] In Sweden, 95% of the women also reported abuse prior to the pregnancy and 4.3% reported serious violence (e.g. attacked with a gun or knife).[228] Violence during pregnancy seems to be occurring more often among younger women, especially adolescents. In a survey comparing the prevalence of abuse among pregnant teenagers and adult women, abuse was reported by 20.6% of teens and by 14.2% of the adult women ($p < 0.01$).[229] An Australian study reported the prevalence of domestic abuse to be 29.2% among pregnant teenagers, aged 12 - 17.[230] In yet another study, abuse was reported by 37.6% of pregnant adolescents and by 22.6% of adult women, which was also a significant difference ($p < 0.001$).[231]

The prevalence of abuse may be influenced by the definitions of abuse, the number of times questions are asked about abuse (women being questioned about abuse more than once during a pregnancy, are more likely to admit to abuse[229]), the setting in which questioning takes place and the population studied.[224,232] Although these factors have the potential to greatly influence statistics, the prevalence of abuse reported across countries is remarkably similar.[232]

According to the rates of violence reported during pregnancy, it is more common than other obstetric complications, such as gestational diabetes or pre-eclampsia.[224] Abuse before or during pregnancy can therefore pose an enormous threat to maternal physical and emotional health and can even lead to the death of the mother, fetus or both.

3.2.4.1 Obstetric risk factors

Pregnant women who have experienced abuse are more likely to delay seeking antenatal care.[231,233,234] A study conducted in Maryland and Texas, reported that among teenage and adult women, significantly more women who reported abuse booked for antenatal care in the third trimester than women who were not abused ($p < 0.001$ for teenagers and $p = 0.007$ for adult women).[229] Data from the PRAMS trial revealed that abused women were almost two times more likely than other women to enter antenatal care after 20 weeks of gestation.[234]

A history of violence is also associated with insufficient weight gain, a history of STI's, vaginal and cervical infections, urinary tract infections, anaemia and antepartum haemorrhage.[229,231,235] Domestic abuse has also been linked to hyperemesis, false labour and unresolved antenatal admissions.[224] As abused women are more likely to have unwanted or mistimed pregnancies, they often seek to terminate their pregnancies.[235] In a survey among women seeking elective termination of their pregnancies, the prevalence of abuse was found to be 39.5%.[236] The abused women in this study were more likely to report relationship problems as the reason for the termination than non-abused women. Abused women were significantly less likely than non-abused women to inform their partners of the pregnancy or to have their support or involvement in the decision to terminate.[236]

3.2.4.2 Adverse pregnancy outcome

Violence before or during pregnancy has been associated with a number of adverse pregnancy outcomes. These include miscarriage, stillbirth, preterm delivery, low birthweight and placental abruption.[174,229,237,238,239,240] In a study among 401 pregnant women who completed three interviews during their antenatal care (violence data was obtained at the third interview) only 34% did *not* experience verbal or physical violence from their spouse of family members during their pregnancies.[240] Among these women 16%

experienced moderate physical violence (e.g. "push, grab or shove you") and 14% experienced severe acts of violence (e.g. "kick, bite or hit you with a fist" or "beat you up"). Violence was strongly correlated with preterm birth. Compared to the women who did not suffer from violence, for the group who experienced moderate violence, the risk of PTD increased to 15.4% and an increased risk of 17.2% was calculated for those women who experienced severe violence.[240]

The most consistent finding has been among studies on intimate partner violence and LBW, suggesting that violence during pregnancy may substantially contribute to LBW, a major cause of neonatal morbidity and mortality.[229,231,241] In a meta-analysis of eight published studies from North America and Europe, Murphy *et al*. reported a significant, association between abuse during pregnancy and LBW (OR 1.36, 95% CI 1.06 – 1.75).[238] In a case-control study from a developing country, mothers of newborn babies weighing less than 2500 grams were almost four times more likely than women who delivered babies weighing 2500 grams or more to have experienced physical abuse during their pregnancies (22% vs. 5%; OR 3.98, 95% CI 1.7 – 9.31). This finding was after controlling for age, parity, smoking and socioeconomic status and therefore suggests that physical abuse during pregnancy is a strong, independent risk factor for LBW.[242] A causal interpretation of the association between violence and LBW, estimated that 16% of the LBW in this study population could be attributed to physical abuse by an intimate partner during pregnancy.

The exact aetiology through which violent experiences can bring about these adverse outcomes remains unclear.

3.2.4.3 Trauma

During pregnancy, women who are in an abusive relationship are more likely to be struck on the abdomen.[226] Such trauma can directly result in placental abruption, uterine contractions or PROM with subsequent PTD and, depending on the gestational age of the fetus, even fetal loss.[224] In a study to evaluate pregnancy outcome after blunt abdominal trauma, Pak *et al*. found a significant difference in peripartum complications between women who reported domestic violence and those who experienced other forms of trauma to the abdomen, e.g. motor vehicle accident. Women who reported domestic abuse were more likely to have PROM, placental abruption, PTL and meconium-stained amniotic fluid.[174]

3.2.4.4 Stress

Another possibility through which violence can lead to adverse pregnancy outcome is through increased levels of maternal stress and anxiety. Stress results in increased levels of maternal CRH levels and immunological changes, which may lead to PTL, PTD and LBW (discussed in Chapter 2). Abused women are also more prone to suffer from severe depression and PTSD.[243] A recent South African-based case-control study, reported that battered women were significantly more likely to suffer from major depression and PTSD ($p < 0.0001$ in both instances).[244] The abused women were also more likely to have attempted suicide ($p < 0.0001$) and there was a tendency towards increased substance abuse among them ($p = 0.06$). However, those women who were diagnosed with PTSD, where the violence suffered was found to be more severe and to more often include sexual abuse, were more likely to have abused substances.[244] In another South African study, it was confirmed that women who experienced domestic violence were more likely to have attempted suicide ($p < 0.001$).[245] A possible explanation for this self-destructing behaviour is that the cognitive focus is constricted and these women are not able to see any positive way of dealing with such a

situation.[245] These results are similar to that of an American study that described these characteristics as "The Battering Syndrome".[188] A comparison of the characteristics of PTSD and the "battering syndrome" is given in Table 3.2. [194]

Table 3.2 Comparison of the characteristics of post-traumatic stress disorder and the battering syndrome.

Post-traumatic stress disorder	Battering Syndrome
The person experienced an event that involved or threatened death, a serious injury or a threat to physical integrity of self or others.	Deliberate and repeated physical or sexual assault experienced by a woman at the hands of an intimate partner.
The person's response involved intense fear, helplessness or horror.	The woman responds with terror, entrapment and helplessness.
The traumatic event is persistently re-experienced, such as through dreams or distressing recollections.	If the woman remains in the relationship, the re-experience may be real, rather than recalled.
Psychological reactivity occurs on exposure to internal or external cues, symbolic of the traumatic event.	The woman feels anxious and isolated (or alone) and reacts to any expression of anger or threat by cowering or attempting to placate the abuser.
The person persistently avoids stimuli associated with the trauma; responses are numbed.	The woman attempts to avoid arousing the anger of the abuser and tries to please him; she exerts effort to control situations to avoid abuse.

Table 3.2 Continued	
The person has persistent symptoms of increased arousal, such as difficulty sleeping, hypervigilance and exaggerated startle response.	The woman is alert to signs of increasing tension in the abuser during the "tension-building" stages; she withdraws from interaction.

3.2.4.5 Smoking

Abused women are more likely to smoke cigarettes and to use alcohol or drugs during pregnancy than non-abused women, which is a way that violence can *indirectly* affect pregnancy outcome.[226,233,246]

McFarlane *et al*. found physical abuse, smoking and alcohol or drug use to be significantly related to low birthweight.[233] Smoking was significantly associated with physical abuse among white and African American women, with a trend towards significance among Hispanic women. Alcohol and drug use was significantly associated with abuse only among African American women. Although not significant, white and Hispanic women who were abused also reported more alcohol and drug use than those who were not abused. There is a highly significant relationship between smoking and alcohol or drug use among all ethnic groups ($p < 0.0001$). A multiple regression analysis was done in order to determine the variance in birthweight accounted for by abuse, smoking and alcohol or drug use. Overall, the three predictors were significant ($p < 0.001$).[233]

However, physical abuse did not exclusively contribute significantly to the low birthweight and the results varied between the ethnic groups. Alcohol or drug use, which was highest among abused African American women (42.1%), contributed significantly to LBW in this group, whereas for white abused women, smoking had the highest prevalence (59.6%) and was significantly associated with LBW. Hispanic women who were abused had the lowest

prevalence of smoking (6.8%) and alcohol or drug use (2.3%), with no significant effect on birthweight, suggesting a dose-response relationship.[233]

These findings are very likely the result of abused women turning to substance use and abuse in order to cope with the profound psychological stress associated with abuse. However, the type and quantity of substances used and abused seem to differ between cultures, which may explain the differences in effect of smoking, alcohol and drugs on birthweight found in this study. It has been reported that among Spanish populations, domestic violence is widely accepted as part of their culture[184], which may explain why the Hispanic women smoked less and used less alcohol or drugs in this cohort. They may more readily accept abuse as "normal" and therefore be less likely to turn to substance abuse as a coping mechanism.

A study on the association of stress and smoking during pregnancy found specific psychosocial differences between women who continued to smoke during pregnancy and those who quit or never smoked.[247] Women who continued to smoke had significantly higher levels of stress than those who quit or never smoked. Of these stressors include financial difficulties ($p = 0.0002$), problems with the family ($p < 0.001$) and domestic violence ($p < 0.001$).[247]

Maternal cigarette smoking during pregnancy has also been associated with intrauterine growth restriction (IUGR), prematurity, abruptio placentae, PPROM and lower folate levels.[175,248,249,250] Lindley and colleagues demonstrated that smoking during pregnancy resulted in reduced birthweight, crown-heel length and head circumference, with the effects being more severe with heavier smoking ($p < 0.001$).[248] According to Chan *et al.*, the prevalence of smoking among pregnant Aboriginal women is 57.8% and 24% among non-Aboriginal women. The relative risk was elevated among the Aboriginal women of having a PTD (OR 1.64; 95% CI 1.51 – 1.80), a growth

restricted baby (OR 2.28; 95% CI 2.14 – 2.43) or a LBW baby (OR 2.52; 95% CI 2.29 – 2.76).[249]

A meta-analyses of the effects of smoking during pregnancy found the pooled OR for abruptio placentae (eight studies included) to be 1.62 (95% CI 1.46 – 1.77). The same study found a pooled OR of 1.7 (95% CI 1.18 – 2.25) for PPROM in women who smoke during pregnancy (six studies included).[250]

In a Norwegian population-based, prospective study over seven years, which included 7236 consecutive pregnancies, 25.4% of the women admitted to daily cigarette smoking.[251] The incidence of PTD in that population was 6%. After adjusting for confounding factors, there was an association between smoking and PTD, but it was only statistically significant among parous women (OR 1.88; 95% CI 1.39 – 2.54) and appeared to be dose-dependent.[251]

A study from Wales was conducted to determine relationship between maternal smoking pregnancy outcome, concentrating on stillbirths and infant death up to one year of age.[252] Among 16250 births there were 608 stillbirths and 634 infant deaths. Among mothers of babies who died, the smoking rate was 37.8%, compared to 27.2% in mothers of those who survived ($p < 0.0001$). The odd ratio for unexplained stillbirths was 1.72 (95% CI 1.38 – 2.13), for intra-uterine deaths due to abruptio placentae, 2.07 (95% CI 1.29 – 3.31) and for sudden infant death syndrome ("cot death") the OR was 4.48 (95% CI 3.05 – 7.69).[252] Maternal smoking was also associated with death due to infection, with a smoking rate of 58% (OR 3.7; 95% CI 2.23 – 6.13). Infections included pneomonia, bronchiolitis, group B streptococcal infections, chorioamnionitis and congenital infections.[252] In this study maternal smoking and fetal or infant deaths were both strongly associated with lower socioeconomic class ($p < 0.0001$ for both analysis).

Homocysteine is an intermediary metabolite of the essential amino acid, methionine.[253] Hyperhomocysteinaemia can be caused by genetic mutations or deficiencies of vitamin B_6, vitamin B_{12} or folate.[254] Folate and homocysteine are linked in the same metabolic pathway and are inversely related, such that, if folate concentrations are low, homocysteine will be high. Hyperhomoceysteinaemia has been associated with an increased risk of neural tube defects, abruptio placentae, IUGR, miscarriage and stillbirth.[253,254] The hypotheses associated with hyperhomocysteinaemia and adverse pregnancy outcome include: the atherogenic effect of hyperhomocysteinaemia leading to the cirdulatory disturbances in the placenta, the deficiencies of B-vitamins, resulting in elevated total homocysteine concentrations, and the direct adverse effects of these deficiencies.[175] Serum homocysteine levels are elevated in over 95% of people with folate or vitamin B_{12} deficiency.[253] Smoking has been associated with elevated levels of serum homocysteine, in men and nonpregnant women[255,256,257], leading to the hypothesis that smoking during pregnancy may lead to hyperhomocysteinaemia, low folate levels and thus adverse pregnancy outcome.

In a study to determine whether smoking during pregnancy decreased folate levels, McDonald *et al.* found that pregnant women who smoked had significantly lower serum folate concentrations ($p = 0.001$) than pregnant women who did not.[254] Red cell folate concentrations were also lower in the smokers, although not significantly, and the homocysteine levels were not significantly different between the two groups. A study from The Netherlands reported that folate levels of women who smoked during pregnancy were significantly lower than those of non-smokers during the last 30 weeks of pregnancy.[253] Vitamin B_{12} levels did not increase or differ significantly between the two groups during the course of gestation. The shift in homocysteine levels during pregnancy was not significant in either of the groups, but the homocysteine levels of the smoking women were significantly elevated from 21 weeks of gestation.[253] Pagán *et al.* also reported

significantly lower levels of folate in smoking pregnant woman at 30 weeks, with no difference in homocysteine levels.[258] The increase in maternal plasma volume during pregnancy may be a possible explanation for the relative stability in homocysteine concentrations.[259]

3.2.4.6 Alcohol use

Over half of American women of childbearing age reported consuming alcohol within the past month.[260] One in seven reported consuming five or more drinks on one drinking occasion (binge drinking) at least once during the same period. Prenatal alcohol exposure is a leading cause of neurodevelopmental deficits in children and, together with fetal alcohol syndrome (FAS), can cause substantial, life-long intellectual, cognitive and psychosocial impairments.[260,261] People with FAS appear to differ from those with other types of mental retardation because of additional problems in the social domain, e.g. poor judgment and distractibility.[262] These social deficits in later life have been linked to abnormal attachment behaviour in infants with FAS.[261]

Women who are fertile, drink alcohol and have unprotected intercourse are at risk for an alcohol-exposed pregnancy.[260] Women who experience intimate partner abuse may be at even higher risk for an alcohol-exposed pregnancy, since abused women are more likely to be younger[228,230,263], to drink alcohol[188,246] and to not use contraception.[183] In a survey to define the characteristics of women at risk for such a pregnancy, recent physical abuse was defined as one of the risk factors.[260] Of the other risk factors included smoking, mental health treatment and having multiple sex partners. These factors have, in turn, also been associated with abuse.

Several studies have evaluated the relationship between maternal alcohol consumption and pregnancy outcome, especially with regards to PTD, LBW and IUGR.[264,265,266] One study found mild drinking (defined as 0.1 – 0.25

ounces of absolute alcohol per day) during early pregnancy to be protective against IUGR, but both light and mild to moderate drinking during the third trimester was associated with a significant increase in the risk for PTD (OR 2.88; 95% CI 1.64 – 5.05 for light drinking and OR 2.96; 95% CI 1.32 – 6.67 for mild to moderate drinking).[264] Kesmodel *et al*. found only those pregnant women with an alcohol intake of 10 or more drinks per week, as reported at 16 and 30 weeks, to be at a significant increased risk for PTD, after controlling for confounding factors.[265] In contrast, Yang *et al*. found no evidence of an independent effect of moderate maternal alcohol consumption (defined in this study as < 14 drinks per week) on the risk for IUGR.[266] Their results are only suggestive of an increased risk for IUGR among women who drank more than 14 drinks per week at the time of conception and during the first trimester of pregnancy.

In contrast, Mittendorf *et al*. found that alcohol use during pregnancy increased the length of gestation.[267]

In addition to the risk of being born preterm to a mother who drinks during pregnancy, these infants have an increased risk of perinatal brain injury.[268] A study was conducted among 349 infants born before 31 weeks and who received at least one cranial ultrasound. The mothers of these babies were questioned about antenatal alcohol consumption in a postpartum interview. After controlling for potential confounding factors, infants of women reporting high alcohol use (seven or more drinks per week or more than three drinks per occasion) were at increased risk of developing isolated brain haemorrhage (OR 5.5; 95% CI 1.2 – 24.7), any brain haemorrhage (OR 6.7; 95% CI 1.8 – 26.4) or white-matter damage (OR 9.5; 95% CI 1.9 – 46.4).[268]

Unfortunately, findings from studies assessing the risk of alcohol use during pregnancy have not been consistent, which is probably due to differences in study methods and especially the assessment of alcohol consumption (the four studies included in this review each used a different measure). The control of potential confounding factors, populations studied and sample size

may also contribute to these differences. Even though the evidence for adverse pregnancy outcome associated with alcohol use is not very strong, the long-term health effects that it can have on the fetus have cannot be ignored.

3.2.4.7 Violence and maternal deaths

Domestic violence during pregnancy has also been identified as a risk factor for maternal death.[183,224,232] Of all the injury-related (intentional or unintentional) maternal deaths referred to the Department of Forensic Medicine in Maputo during a five-year period, 75% were associated with violence, i.e. homicide, suicide and self-induced abortion.[269] Young women (< 25 years old) comprised 59% of the maternal deaths due to injury and 47% of all maternal deaths in Maputo.[269] Pregnant or puerperal women in Bangladesh, aged between 15 and 19 years, were nearly three times more likely to die from injuries than non-pregnant women of the same age and were also at significantly higher risk than older women.[270] Homicide was the most important cause of injury-related deaths in Maputo (37%), correlating with findings from an American study (35.5%).[271] In this study the relative risk for injury-related maternal death was 1.7 (95% CI 1.4 – 2.2) when comparing nonwhites with whites.[271] Traditional thinking that these deaths are unrelated to pregnancy might not be correct. As abused women may be more likely to enter antenatal care late[231,233] or not at all, they are at increased risk of direct or indirect obstetric death.[271] Suicide deaths may causally be related to an unplanned pregnancy or postpartum depression. The risk of homicide has also been reported to be higher among pregnant than non-pregnant women.[271]

3.2.5 GYNAECOLOGICAL PROBLEMS

"Gynaecological problems are the most consistent, longest lasting and largest physical health difference between battered and non-battered women."
THE LANCET, 2002[232]

Sexual and physical violence appears to increase women's risk for many common gynaecological disorders, some of which can be debilitating.[183] A good example is chronic pelvic pain (CPP), which may account for as many as 10% of all gynaecological visits and up to 25% of all hysterectomies.[183,272] Although CPP is commonly caused by adhesions, endometriosis or infections, about half the cases of CPP do not have any identifiable pathology.[183] Several studies have found that women suffering from CPP are more likely to have a history of childhood sexual abuse, sexual assault and physical and/or sexual abuse by their partners.[272,273,274,275] In testing this hypothesis, Schei reported that almost half (48%) of the physically abused women included in the study ever suffered from pelvic pain vs. 21% of the non-abused women ($p < 0.001$).[275] Past trauma may lead to CPP through unidentified injuries, stress or by increasing a woman's susceptibility to somatisation, i.e. the expression of psychological distress through physical symptoms.[183] Childhood sexual abuse, which has been linked to high-risk sexual behaviour in adolescence and adulthood, may be another cause of CPP due to pelvic inflammatory disease, in turn resulting from STI's.[183,207,208]

Other differential symptoms and conditions may include:[188,273,276,277,278,279]

- STI's
- Vaginal infection
- Irregular vaginal bleeding
- Dysmenorrhoea
- Menorrhagia
- Fibroids

- Sexual dysfunction (e.g. dyspareunia, conflicts over frequency of sex, anorgasmic)
- Urinary tract infections

In a population-based study in the USA, victims of abuse were three times more likely than average to present with a gynaecological problem.[188] More serious or a larger number of symptoms may be the result of more severe violence (dose-response effect), whether both physical and sexual abuse was suffered, whether the victim knew the offender and whether there were multiple offenders.[232,280] It has been reported that the combination of physical and sexual abuse (which is the case in 40 – 45% abusive relationships) puts these women at even higher risk for health problems than women who are only physically abused.[273,277] There are consequences of forced sex that could explain the higher incidence of gynaecological problems among abused women.[232] Of these possible mechanisms include:

- depression of the immune system through high levels of stress and depression,
- increased transmission of micro-organisms through vaginal, anal or urethral trauma (directly into the circulation or backflow of bacteria into the urethra),
- men forcing sex on their partners or having unprotected sex with other women and
- controlling acts, such as verbal sexual degradation, refusal to use condoms and refusal to use contraception.

These issues may also partly explain the links between intimate partner violence and STI's, HIV and unintended pregnancies.

3.2.6 EFFECT OF VIOLENCE ON CHILDREN

Conflict between parents is bound to have an effect on their young children. Between 49 and 64% of abused women have reported that their children have

witnessed them being abused.[183,184] Children who witness violence are at increased risk of developing behavioural and emotional problems, such as anxiety, depression, poor school performance, low self-esteem, disobedience and physical health problems.[183] As these children learn to solve conflict with violence, they are also more prone to aggressive behaviour during childhood and adolescence.[183] It has been reported that children who witness their mothers being abused by fathers or stepfathers, are nine times more likely than other children to suffer from learning, emotional and behavioural problems and are seven times more likely to be abused themselves.[184] In a survey among 4127 Californian men, 11% had grown up with a battered mother and of those, 71% were also physically or sexually abused.[217]

It has also been suggested that the involvement of children in the violence is a particular source of anguish for a mother, possibly more distressing than her own abuse.[184]

...When he beat me, my daughters would get involved in the fight. Then he would throw them around in his fury and this hurt me, it hurt me more than when he beat me...[184]

Violence may undermine child survival as well.[281] A study from two Indian states reported, after controlling for other influences on infant mortality, that battered women were significantly more likely than other women to have suffered an infant death or pregnancy loss through abortion, miscarriage or stillbirth.[281]

It is not clear exactly how domestic violence affects child welfare and survival. One explanation is that, because violence is associated with LBW, such children are already at risk of morbidity or mortality during infancy and childhood. Another possible factor is that women are unable to keep their children healthy. An American survey reported that abused women were three times more likely than non-abused women to have their daily activities

limited due to depression or sadness, they were more likely to have children under the age of five in the household and were more likely to have limited access to health care. Abused women in this survey were also more likely to report that they could not afford to eat balanced meals (OR 2.2; 95% CI 1.8 – 2.7) and were almost five times more likely to report not being able to afford food on occasion (OR 4.8; 95% CI 3.3 – 6.9).[282]

Alcohol and drug use, which is higher among abused women, may also influence children's health and survival. Mothers who abuse alcohol and drugs are more likely to neglect their children and would rather use money to buy alcohol or drugs than healthy food. Children of adolescent mothers are also more likely to be abused or neglected because of the social, financial and emotional stressors of teenage motherhood.[283] Childhood sexual abuse has been found to be a significant risk factor of subsequent physical abuse of one's own children.[284] Maternal anger was confirmed as a mediator of the relationship between having been sexually abused as a child and the potential of physically abusing one's own children.[284]

3.2.7 WHAT HEALTH CARE PROVIDERS CAN DO

Every woman will at some point need to make use of medical care, even of she is not ill, e.g. a family planning clinic, a routine gynaecologic examination or obstetric care. It has therefore been suggested on numerous occasions that routine questioning on domestic violence be implemented in health care protocols, especially in obstetric care facilities, as pregnancy is the only time when otherwise healthy women have regular contact with health care providers.[182,183,190,226,285] Unless women are asked directly about violence, they are not very likely to volunteer such information.[183] Therefore, routine screening of women for physical and sexual abuse by health care professionals may help identify cases of domestic violence and may even open up a door through which such woman can escape to a new life, safe from physical violence. Any health care provider can make a difference by

routinely asking about abuse.[183] An important first step is to develop a standard way to ask the question for all clients. Some options from the Center for Health and Gender Equity include:[183]

Introducing the question:
"Because violence is common in women's lives, we have begun asking all clients about abuse."
Asking indirectly:
"Your symptoms may be related to stress. Do you and your partner fight a lot? Have you ever gotten hurt?"
Asking directly:
"Has your partner or ex-partner ever hit you or physically hurt you?"
"Did you ever have any upsetting sexual experiences as a child?"

A very simple and short questionnaire that has been developed by McFarlane *et al.*, has been found to be very effective as a screening tool for identifying abuse among women (see Appendix 1).[286]

Routine questioning about domestic violence should preferably not be viewed as "screening", but rather as uncovering and reframing a hidden stigma.[287]

When introducing these or similar questions to a client, care should be taken to be empathetic and respectful of the woman's privacy and not to appear judgmental. Implementing routine screening into general practice will require time, training of staff and, most importantly, adequate community resources for referral. Where such infrastructures are not available, screening for violence may do more harm than good in that the woman, expecting help, may feel disappointed or let down and thus be less likely to disclose violence when asked in the future.

Where routine screening cannot be implemented in practice as yet, it is important to be alert for signs and symptoms that are sometimes associated

with physical and sexual abuse and to only approach those women. These symptoms are listed in Table 3.3.[183]

Table 3.3 Signs and symptoms of physical and sexual abuse in women

Physical abuse	Sexual abuse
Chronic vague complaints that have no obvious physical cause	Pregnancy under the age of 14
Injuries that do not match the explanation of how they occurred	STI's in children or young girls
A male partner who is overly attentive, controlling or unwilling to leave the woman's side	Vaginal itching or bleeding
Physical injury during pregnancy	Painful defecation or urination
Late entry into antenatal care	Abdominal or pelvic pain
A history of attempted suicide or suicidal thoughts	Sexual problems, including lack of pleasure
Delays between injuries and seeking treatment	Vaginismus (spasms of the muscles around the opening of the vagina)
Urinary tract infection	Anxiety, depression or self-destructive behaviour
Chronic irritable bowl syndrome	Sleeping problems
Chronic pelvic pain	A history of chronic, unexplained physical symptoms
	Having difficulty with or avoiding pelvic exams
	Problems with alcohol or drugs
	High-risk sexual behaviour
	Extreme obesity

Several studies among very different populations have reported that women are very much in favour of routine questioning about domestic abuse.[287,288,289] A British study reported that 99% of 718 pregnant women found it acceptable to be asked about domestic violence by a midwife.[288] Very few women were offended by the questions or felt distressed by the study.

"All health professional should ask. You never know what happens behind closed doors. It might look to you and me like the perfect family, but once the door is shut anything could be going on in there."

Some women said that being asked about domestic violence helped them to think about things differently and assisted them in seeking help and making a decision about their situation.[288]

"It made me leave him. She gave me a card and said, 'You don't have to stay in that situation. I wish you make the right decision for you and your baby.' That was something that really pushed me up."

Among Swedish women, 80% found routine questioning acceptable, 13% were uncertain and only 3% found such questions unacceptable.[289] A cross sectional survey among 22 Irish general practitioners (urban and rural), reported that 78% of women were in favour of routine questions on abuse and 13% were uncertain.[287] In the survey, 39% of the women had experience one or more episodes of violent behaviour by a partner and of those women, only 12% reported that their doctor had previously asked them about partner abuse.

The majority of physicians providing obstetric and gynaecological care do not screen for current or past domestic abuse among their patients.[290] In a survey among 6568 physicians, only 14.6% responded to mailed questionnaires and among those, only 18.9% of male doctors and 25.9% of female doctors routinely screened for abuse. Almost 40% of these doctors indicated that they had no education in domestic violence and 71% reported

this lack of training to be the most important barrier to screening. Other barriers were: type of patient in 46% ("middle- and upper-class women are unlikely to be victims"), lack of time (39.2%), inability to help (34.3%), personal history of abuse (13.1%), fear of offending the women (15.2%), and feeling abuse was not a medical problem (13.9%).[290] Unfortunately, because of the low response rate in this study, the true number of physicians screening for abuse may be much lower. These findings also emphasise the importance of implementing the issues of gender-based violence into all areas of medical training.

The following guidelines were prepared by the Center for Health and Gender Equity in order to promote nonviolent relationships:[183]

Health workers:

- Educate themselves about physical, sexual and emotional abuse and explore their own biases, fears and prejudices.
- Provide supportive and non-judgmental care to victims of violence.
- Ask clients about abuse in a friendly, gentle way.

Leaders of reproductive health programs:

- Establish policies and procedures to ask women clients about abuse.
- Establish protocols that clearly indicate appropriate care and referral for victims of abuse.
- Promote access to emergency contraception.
- Lend facilities to women's groups seeking to organise support groups and have meetings.

Community and religious leaders:

- Urge understanding, compassion and concern for victims of violence.
- Challenge religious interpretations that justify violence and abuse of women.
- Make their houses of worship available as temporary sanctuary for women in crisis.
- Support the effort of abused women to leave relationships that put them at risk.

- Integrate discussions on healthy relationships and alternatives to violence into religious education programs.

The mass media:

- Respect the privacy of victims of rape by not printing their names without permission.
- Avoid sensationalising of cases of violence against women, place events in their proper context and use them as an opportunity to educate and inform.
- Provide free airtime or space for messages about gender violence and announcements of available services.
- Reduce the amounts of violence portrayed on television
- Develop socially responsible radio and television programming that depicts equal and non-violent relationships between men and women.
- Develop programming that creates public dialogue about sexual coercion, rape and abuse.

Parents:

- Refrain from arguing in front of their children.
- Teach their children to respect others and themselves.
- Encourage health, safety and intellectual development of their children and encourage their self-esteem.
- Teach children non-violent ways to resolve conflicts.
- Talk to their children about sex, love and interpersonal relationships, emphasising that sex should always be consensual.

3.3 CONCLUSION

Violence against women is clearly an enormous problem that is not "just going to go away" and women everywhere are at risk. Women who are exposed to violence are robbed of their ability to trust others, their self-respect, a sound mind and a healthy body. In order to cope with the stress and shame, these women often turn to alcohol, drugs, cigarettes and casual sex to help them through difficult times and more often than not end up in a worse state of mind. Addictive behaviours unfortunately need to be fed and selling sex will

pay. Having casual sex without protection will likely add yet another neglected baby, maybe even a HIV-infected baby, to the millions around the world who are already fighting to survive. These children are also at risk of being abused by a frustrated teenage mother who is being denied her dream of a good education, a respectable career and a loving husband. A woman drowning her sorrows with alcohol, nicotine and drugs places herself at risk of repeated abuse, thus creating a vicious cycle that is very difficult to break.

Married women are very often in an almost impossible position to leave an abusive husband. Where will she go? What about money? What will her family say? What about the children? It is often said that the best gift a father can give his children is to love their mother. Maybe the best gift a mother can give her children is to leave their abusive father. Children should not learn to kill, steal and destroy, but to love, and love abundantly.

...Once, when I was recovering, because he had beaten me and he had left my eyes swollen and black, my daughter came up to me and said, "Mommy, you look like a monster" and she began to cry... It hurt me so much. It wasn't so much the blows I had, but what really hurt me, was her sobbing and the bitterness that she was feeling. It changed everything for me when I realised that I was hurting my daughters by staying in a marriage with no future.

Ana Cristina, Nicaragua[184]

One has only to look at the results from the numerous studies done around the world, to acknowledge that gender-based violence is the root of a substantial amount of reproductive health problems, making it a priority health issue.[182] There are, unfortunately, no easy answers. Health care workers cannot solve this problem alone, but with sensitivity and commitment, they can begin to make a difference. Ending physical and sexual violence requires long-term commitment and strategies involving all parts of society.

CHAPTER 4: IS DOMESTIC VIOLENCE A RISK FACTOR FOR PRETERM BIRTH?

4.1 INTRODUCTION

The incidence of preterm birth at Tygerberg Hospital is 20.3% (Tygerberg Hospital database, unpublished data). To date no definite cause for PTL could be identified, which is mainly due to the multifactorial etiology of PTL.[79]

It is estimated that one in every three women will be psychologically, physically or sexually abused at some time during her lifetime.[183] Exposure to violence unfortunately carries with it much more than just the physical scars that destroys any evidence of abuse once thy have healed. Much worse is the fear, anxiety and depression that do not come in visible shades of blue, but manifests itself in the form of risk-taking behaviour. Such behaviour can lead to an unwanted pregnancy, often at a time when the woman is not ready or able to cope with the responsibility or believing that she has to stay in an abusive relationship because of the baby.

Violence has been associated with adverse pregnancy outcome, including preterm birth, and it may well be that in a community where violence is not uncommon, exposure to violence may place pregnant women at risk of delivering preterm. The community served by Tygerberg Hospital is mainly from disadvantaged background and many are subjected to violence, either in their own homes or on the streets where there is a lot of violent activity between "street-gangs". As violence has been associated with stress, anxiety and substance abuse, it may thus indirectly play a role in adverse pregnancy outcome.

Caring for a preterm baby in such circumstances is also a challenge. These babies often need more attention and special care than most parents can provide

and in a poverty-stricken community, these babies are therefore at high risk of being neglected. The inevitable frustration resulting from the extra financial burden may also place the mother at risk of being abused. Domestic violence is therefore not a subject that can be separated from reproductive health, including pregnancy outcome.

4.2 OBJECTIVE

This study was undertaken to determine whether women in the community served by Tygerberg Hospital who are victims of violence are at greater risk for preterm delivery. These women are mainly Coloured and of low socioeconomic background.

4.3 METHODS

In a comparative study, two different groups of women were approached and invited to participate in the study. The first group (preterm labour or PTL group) consisted of women who were admitted to Tygerberg Hospital for suppression of preterm labour between 24 and 33 completed weeks of gestation with, or without the rupture of membranes. A diagnosis of PTL by the responsible registrar was obtained from each woman's file. Also entered into the first group, were those women who had delivered spontaneously, without any known reasons, between 24 and 33 weeks completed weeks' gestation, regardless of their obstetric history. Included in this group as well, were women who experienced a placental abruption before 34 weeks in the absence of any hypertensive disorder, where the blood clot covered more than 15% of the placental surface. Excluded from the PTL-group were women with preterm delivery due to known reasons, such as multiple pregnancy, placenta praevia, polyhydramnios and induction of labour for pre-eclampsia or other medical indications.

The second group referred to as the low-risk (LR) group, included women who received their antenatal care at a local midwife obstetric unit (MOU). These

women are considered to be at low risk for pregnancy complications, including PTL, according to their obstetric history. As Tygerberg Hospital is a tertiary institution, the women attending the antenatal clinics there are mostly those who are referred from the local MOU's and who are at high risk for pregnancy complications. Also, the low risk women normally deliver at the MOU, unless there are unforeseen complications in which case they are referred to Tygerberg Hospital. It was therefore mainly for these reasons that women attending a local MOU were chosen for the comparison group.

A questionnaire was designed and administered to the women by J.S., as the literacy of the women in our population varies from no schooling at all to tertiary education. The questionnaire consisted of three parts:

1. The data sheet, including questions of obstetric history, demographic information, information of the index pregnancy and outcome of the pregnancy and neonate (Appendix 1).
2. The second part contained questions concerning the lifestyle, including questions on smoking, alcohol (including the quantity) and drug use. Neither the extent of alcohol use by the woman's partner, nor of drug use by the woman or her partner, was questioned (Appendix 1).
3. To determine the prevalence of violence in out population, we used the "Abuse Assessment Screen" from McFarlane *et al.*[286], but did not ask the women to identify the areas of injury on a body map. An additional question was added to the questionnaire in order to find out from the women why they thought men abused women (Appendix 2).

Women were recruited for the study between November 2000 and April 2002. In order to locate potential participants, the birth register of the hospital was scanned each morning for any preterm deliveries or placental abruptions before 34 weeks, but after 24 weeks, during the previous 24 hours. These women were located in the different postpartum wards and their files were read to determine the reason for the PTD. Eligible women, who delivered preterm for reasons

unknown, were approached at an appropriate time and taken into any private room available in the ward. Some of the women were only approached after discharge from the postpartum ward, given they were moved to the neonatal "Kangaroo Care" ward, where they stayed with their small babies, providing skin-to-skin contact and breast milk for them.

Also, all the files in the antenatal ward were scanned each day to identify women in the ward who were being suppressed for PTL. These women were located, and approached at an appropriate time (e.g. when labour pains had sufficiently subsided and the woman was feeling more comfortable and allowed to walk about). The questionnaires were administered in any private room in the ward. It was also noted if there were any women in the labour ward who were being suppressed, and these women were then followed up and approached when they were moved to the antenatal ward or, in the case of a subsequent PTD, the postpartum ward. Fortunately, there were women who were successfully suppressed after PTL, they were followed up until delivery and their files were collected in order to obtain the necessary data.

The women who were entered into the LR group were attending a local MOU. Postpartum interviews were difficult to do at this setting, as most of the women were discharged six hours after delivery. Those women who did stay longer all had their babies with them, demanding attention, and were in rooms of four. Lack of privacy was a problem.

Therefore, once a week, on the day of the follow-up antenatal clinic at the MOU, I drove out to interview some of the attending women. As the women arrive at the clinic, they hand in their appointment card at the reception area and receive a number that will determine the order in which they will be seen on that day and assures a "first come, first served" scenario. The two responsible midwives begin at number one and two and then simply call the next number as they progress as the doors to the examination rooms conveniently open into the

waiting area. They keep record of the order in which the women are seen to assure fairness and the women are also very aware of the order in which they are seen.

For the domestic violence study, women were selected randomly from the waiting area. I would first enquire which numbers the midwives were busy with and would call women from the waiting area who's numbers were about 10 ahead, for example, if they were busy at number 21, numbers 30 to 35 would be called to be interviewed. In the case of one of these numbers not being there (e.g. went to the shop), the next number would be called. These women were then interviewed in any private room that was available on that particular day and were followed up until delivery.

Only women who understood and spoke Afrikaans of English were asked to participate in the study. After they had given their written, informed consent, the questionnaire was administered. The questionnaire took about 20 minutes to complete and was administered by one person throughout the trial. The questionnaires were anonymous, but were numbered. The names and folder numbers of the women were listed, together with their particular study number, in a separate list as the pregnancy outcomes still had to be followed up. Not one woman refused to participate in the study.

All the women who admitted to experiencing violence at some time during their lives were offered contact numbers of a local organization that provides counseling and legal help.

Statistical analysis:

The data collected was coded, tabulated and entered into a computer. Statistical analysis was carried out using the Epi Info Statistical Package. The number and percentage of qualitative variables and the mean and standard deviation (SD) of quantitative data were calculated. Comparisons between mean values of

quantitative variables were calculated using the Student's t-test, while the chi-square test was used for qualitative data. A 95% confidence interval (CI) was calculated where applicable. All tests of significance used were at the 5% level of significance.

In addition, we analyzed whether women who experienced violence are at risk for earlier preterm delivery, breaking the gestations at delivery up into < 28 weeks, < 34 weeks and < 37 weeks. We also looked at the primigravidae from both the PTL and LR groups as a single group together (n = 95), in order to determine whether those who admitted to ever experiencing violence, delivered earlier than those who did not experience violence. The primigravidae-only group was analysed without those who had a placental abruption as well (n = 87). Finally, the women in the PTL group who did not have a history of a previous PTD or a placental abruption in the index pregnancy (n = 69) were compared to the LR group in terms of ever experiencing violence, alcohol use and smoking.

4.4 RESULTS

A total of 229 patients were recruited. The PTL-group consisted of 107 women with spontaneous preterm labour and/or delivery (38 with, and 69 without a history of a previous PTD or midtrimester miscarriage) and 23 women with abruptio placentae. In the LR-group there was 99 women.

There was no difference between the two groups in terms of age, parity and gestational age at booking. The PTL group had a significantly higher gravidity, which may be attributed to the higher number of previous miscarriages in the PTL group (Table 4.1).

The total number of admissions for the PTL groups was 124 and there were 87 admissions for suppression of labour for 75 women in this group (Table 4.2).

All patients undergo routine screening for syphilis at our antenatal clinics. In this study the PTL group had significantly more women with a VDRL titer of more than 1:8, which is considered as clinically significant (p = 0.005). The difference persisted when the 23 abruptio-patients were separately compared to the LR group (17.3% vs. 0.01%; p = 0.01). The incidence of syphilis was the same for the abruptio and PTL-only groups (17.3 and 16.8%, respectively).

Table 4.1 Demographic data

	PTL n = 130	**LR n = 99**	**p-value**
Age, years (median and range)	25 (15 – 43)	22 (15 – 38)	0.05
Gravidity (median and range)	2 (1 – 8)	1 (1 –5)	< 0.001
Parity (median and range)	2 (0 – 6)	1 (0 – 5)	NS
GA, weeks (median and range)	18 (5 – 30)	17 (1 – 34)	NS

GA = gestational age at booking, PTL = preterm labour, LR = low risk

Table 4.2 Admissions and antenatal visits

	PTL n = 130	**LR n = 99**	**p-value**
Admissions	89 (68.5%)	12 (12.1%)	< 0.001
Antenatal visits (median and range)	3 (0 –16)	7 (1 – 15)	< 0.001

PTL = preterm labour, LR = low risk

Table 4.3 Prevalence of syphilis

	PTL n = 130	LR n = 99	p-value
VDRL titer < 1:8	9 (6.9%)	2 (2%)	ND
VDRL titer ≥ 1:8	13 (10%)	1 (1%)	< 0.005

PTL = preterm labour, LR = low risk, ND = not done

The mean GA at delivery for the PTL group was 30.5 weeks and 39.4 weeks for the LR group. There were no differences between the two groups with regard to mode of delivery, caesarean section rate or maternal postpartum complications. The mean birthweight for the PTL group was 1577 (± 650)g and 3216 (± 500)g in the LR group.

All 99 babies in the LR group were discharged alive and well, compared to 94 in the PTL group (Table 4.4).

Table 4.4 Neonatal outcome

	PTL n = 130	LR n = 99
Alive	94	99
Miscarriage (< 28 weeks)	12 (3 abruptio placentae)	0
IUD	17 (13 abruptio placentae; 1 intrapartum)	0
NND	7	0

PTL = preterm labour; LR = low risk; IUD = intra-uterine death; NND = neonatal death

Twenty-four babies (23 from PTL group and 1 from LR group) were admitted to the neonatal ICU, with 17 of them requiring ventilation. On discharge, almost half of the preterm babies still needed care at a secondary or primary institution (Table 4.5). The one baby in the LR group who was admitted to the NICU was delivered by caesarean section at 32 weeks for fetal distress after the mother presented with HELLP syndrome.

Table 4.5 Neonatal admissions		
	PTL **n = 130**	**LR** **n = 99**
NICU (n)	23	1
Days (mean ± SD) **(median and range)**	7.1 (±7) 6 (1 – 16)	7
Ventilation (n)	16	1
Total days in hospital **(mean ± SD)** **(median and range)**	11.4 (±12) 8 (1 – 54)	1.7 (±2.5) 1 (1 – 23)
To other hospital (n)	49	1
NICU = neonatal intensive care unit; PTL = preterm labour; LR = low risk		

Questionnaire:

Significantly more women in the PTL group were either married or living with their partners (52.3% and 38.4%, respectively; p = 0.03) Of the LR women, 63.6% were still living with their parents or other family, compared to 44.6% of the PTL group (p = 0.04).

In terms of education, there was no significant difference between the two groups. Almost 60% of the women were unemployed at the time of the interview. In both groups, 6.1% of the women either had a higher education or earned a bigger salary than their partners (Table 4.6).

Table 4.6 Education		
	PTL **n = 130**	**LR** **n = 99**
None (%)	1 (0.8)	0
Primary school only (%)	26 (20%)	16 (16.2%)
High school (%)	92 (70.8%)	75 (75.8%)
Tertiary education (%)	11 (8.5%)	8 (8.1%)
Unemployed (%)	70 (53.8%)	61 (61.6%)
Higher education or salary than partner (%)	8 (6.1%)	6 (6.1%)
PTL = preterm labour; LR = low risk		

The number of women who admitted to smoking cigarettes did not differ between the two groups (Table 4.7). Neither were there any differences in terms of the age when they started or passive smoking.

Table 4.7 Cigarette smoking			
	PTL n = 130	**LR n = 99**	**p - value**
Smokers	73 (56.2%)	55 (55.5%)	0.92
Mean / day (± SD)	5.7 (±4.7)	3.6 (± 1.6)	0.0019
Median / day (range)	4 (1 – 22)	3 (1 – 8)	
Age (years) when started smoking, (median and range)	16 (9 – 30)	16 (12 – 22)	NS
Passive smokers	103 (79.2%)	82 (82.8%)	NS
PTL = preterm labour; LR = low risk; NS = not significant			

The smoking status within the PTL group [abruptio group (n = 23) vs. rest (n = 107)] did not differ significantly (52.2% vs. 57%; p = 0.36), see Table 4.8. There was also no significant difference in term of smoking between the abruptio group and the LR group (52.2% vs. 55.5%; p = 0.14), see Table 4.9.

Table 4.8 Cigarette smoking within the PTL group

	Abruptio group n = 23	Rest of PTL group n = 107	p-value
Smokers	12 (52.2%)	61 (57%)	0.67
Mean / day	4.5	5.9	0.36

PTL = preterm labour

Table 4.9 Cigarette smoking between the abruptio and LR groups

	Abruptio group n = 23	LR group n = 99	p-value
Smokers	12 (52.2%)	55 (55.5%)	0.77
Mean / day	4.5	3.6	0.14

LR = low risk

Forty-three percent of women in the PTL group admitted to alcohol use, compared to 12.1% in the LR group [$p < 0.001$; OR 5.32 (2.53 – 11.4)]. Within the PTL group (abruptio group vs. rest), the difference in alcohol use was not significant (39.1% vs. 43%; $p = 0.73$). Both the abruptio group and the rest of the PTL group drank significantly more than the LR group when analised separately; $p = 0.004$ and <0.001, respectively (Table 4.10).

Table 4.10 Alcohol use between the main groups and sub-groups

	PTL n = 130	LR n = 99	p-value
Alcohol use	55 (43.3%)	12 (12.1%)	< 0.0001 OR 5.32 (2.53-11.4)
	Abruptio group n = 23	**Rest of PTL group n = 107**	
Alcohol use	9 (39.1%)	46 (43%)	0.73
	Abruptio group n = 23	**LR group n = 99**	
Alcohol use	9 (39.1%)	12 (12.1%)	0.004 OR 4.66 (1.48-14.8)
	Rest of PTL group n = 107	**LR group n = 99**	
Alcohol use	46 (43%)	12 (12.1%)	< 0.0001 OR 5.47 (2.55-11.94)

PTL = preterm labour; LR = low risk

Most of the women in both groups admitted to drinking beer and mostly over weekends. Three women in the PTL group and one woman in the LR group drank wine. Of the alcohol users in the two groups, more that a third (67.3%) in

the PTL group admitted to drinking one to five beers per weekend, and 81.8% (9/11) in the LR group. However, 30.8% in the PTL group drank more than five beers per weekend in comparison to 18.2 % in the LR group and one woman in the PTL group drank between three and five beers per day. In each of two groups (PTL and LR), half of the women said that their partners used alcohol (50.8% vs. 52.5%; p = 0.79). Unfortunately, it was not asked how much they drank.

In the PTL group, one woman admitted to using marijuana and one to using both marijuana and mandrax. None in the LR group used narcotics. Significantly more of the partners of the women in the PTL group used narcotics, but also only marijuana and/or mandrax. As the numbers were very small when the different drugs were compared (including 0), the overall number of drug users among the women's partners was used in the statistical analysis (Table 4.11).

Table 4.11 Drug use among women and their partners

	PTL n = 130	**LR n = 99**	**p-value**
Marijuana only	1	0	ND
Marijuana and Mandrax	1	0	ND

Table 4.11 Continued			
Partner drug use:			
Marijuana only	9	0	ND
Marijuana and Mandrax	4	2	ND
Mandrax only	2	0	ND
Total	15 (11.5%)	2 (2%)	0.006
PTL = preterm labour; LR = low risk; ND = not done			

ABUSE ASSESSMENT SCREEN

The only question that showed a significant difference between the two groups, was the first one.

1. Have you ever been physically or emotionally abused by your partner or someone close to you?

Table 4.12 Women who ever experienced violence		
PTL **n = 130**	**LR** **n = 99**	**p - value**
77(59.7%)	40 (40.4%)	0.0038 OR 2.18 (1.24 – 3.86)
PTL = preterm labour; LR = low risk		

2. Within the last year, have you been hit, slapped, kicked or otherwise physically hurt by someone?

Table 4.13 Women who experienced violence during the year preceding the interview		
PTL n = 130	**LR n = 99**	**p - value**
41 (31.7%)	26 (26.3%)	0.36 OR 1.31 (0.70 – 2.44)
PTL = preterm labour; LR = low risk		

3. Since you've been pregnant, have you been hit, slapped, kicked or otherwise physically hurt by someone?

Table 4.14 Women who experienced violence during the pregnancy		
PTL n = 130	**LR n = 99**	**p - value**
28 (21.5%)	12 (12.1%)	0.059 OR 2.01 (0.91 – 4.48)
PTL = preterm labour; LR = low risk		

The question on whom the perpetrators were, within the last year or during the pregnancy, did not show any significant difference between the groups (Table 4.15).

Table 4.15 Different perpetrators to women who experienced violence

	PTL group n = 130		LR group n = 99	
	During last year	**During pregnancy**	**During last year**	**During pregnancy**
Husband	6 (14.6%)	4(14.3%)	5 (19.2%)	2 (16.7%)
Ex-husband	1 (2.4%)	1 (3.6%)	1 (3.8%)	0
Boyfriend	17 (41.5%)	11 (39.3%)	12 (46.2%)	5 (41.7%)
Father	2 (4.9%)	1 (3.6%)	0	0
Stranger	3 (7.3%)	2 (7.1%)	2 (7.7%)	1 (8.3%)
Other	15 (36.6%)	10 (35.7%)	6 (23.1%)	4 (33.3%)
Multiple	2 (4.9%)	1 (3.6%)	0	0

PTL = preterm labour; LR = low risk

For those women who experienced violence during the past year, the events were evaluated by scale (see Appendix 2).

Table 4.16 Scale of most severe violence suffered (within last year)			
Scale	**PTL group n = 41**	**LR group n = 26**	**p-value**
No. 1 (Threats, etc.)	0	0	
No. 2 (Slapping, etc.)	19 (46.3)	11 (42.3%)	ND
No. 3 (Punching, etc.)	6 (14.6%)	12 (46.2%)	ND
No. 4 (Beaten up, etc.)	5 (12.2%)	0	
No. 5 (Permanent injury)	0	1 (3.8%)	
No. 6 (Weapon)	9 (22%)	1 (3.8%)	0.046
PTL = preterm labour; LR = low risk; ND = not done			

There was no significant difference between the two groups with regards to forced sexual activity within the past year, nor in terms of fear for their partners or anyone else who may have abused them (13.8% vs. 7.1%; p = 0.1).

As to why the women thought men abused women, out of the 229 women, 54 (24.5%) either did not give an answer or did not know. Of the remaining 175, 20% thought that women deserved to be beaten if they did not obey their partners. Other reasons given were: alcohol (24.6%), jealousy (17.7%), he sees other women (6.9%), takes frustration out on her (8.6%) and cowardliness (4.6%).

Additional analysis

In the PTL group (n = 130), those women who experienced violence were at no greater risk for earlier preterm delivery, not even if the experience was within the past year or during the index pregnancy. When we looked at the primigravidae from both groups together (n = 95), we found that for those who admitted to ever experiencing violence, there was a trend to deliver before 28 weeks gestation (Table 4.17).

Table 4.17 Preterm delivery at different gestations for primigravidae only

	Primigravidae (n = 95)		
	Violence ever n = 39	**Violence never n = 56**	**p-value**
< 28 weeks	7 (17.9%)	2 (3.6%)	0.03 (Fischer) OR 5.9 (1.03-44.1)
< 34 weeks	21 (53.8%)	21 (37.5%)	0.1
< 37 weeks	23 (59%)	23 (41.1%)	0.08

PTL = preterm labour; LR = low risk

In the primigravidae group without the abruptio's, there was a trend to deliver earlier at each of the three gestations in the group who ever experienced violence (Table 4.18).

Table 4.18 Preterm delivery at different gestations for primigravidae without abruptio-group

	Primigravidae without abruptio (n = 87)		
	Violence ever n = 37	**Violence never n = 50**	**p-value**
< 28 weeks	7 (18.9%)	2 (4%)	0.03 OR 5.6(0.9-42)
< 34 weeks	19 (51.4%)	15 (30%)	0.04 OR 2.46(0.93-6.58)
< 37 weeks	21 (56.8%)	17 (34%)	0.03 OR 2.55(0.97-6.74)

PTL = preterm labour; LR = low risk

Those women who delivered preterm without a history of a prior preterm delivery or with a placental abruption (n = 69), showed higher incidences of ever experiencing violence, alcohol use and smoking, when compared to the LR group (Table 4. 19).

Table 4.19 Comparison between women in the PTL-group without a history of PTD or abruptio placentae with the women in the LR-group			
	PTL n = 69	**LR n = 99**	**p-value**
Violence, ever	41 (59.4%)	40 (40.4%)	0.015 OR 2.16 (1.14–4.2)
Alcohol	30 (43.5%)	12 (12.1%)	<0.001 OR 5.58 (2.4-12.9)
Smokers	38 (55.1%)	55 (55.5%)	NS
Number/day (mean)	5.07	3.6	0.026
PTL = preterm labour; LR = low risk; NS = not significant			

4.5 DISCUSSION

The two groups of women did not differ in terms of age, parity or gestational age at booking. There were significantly more antenatal admissions and less antenatal visits for the PTL group, which was expected, as admission for PTL was one of the inclusion criteria. The women who gave birth preterm had a significant higher incidence of syphilis. Infection has been strongly associated with PTL as well as with low socioeconomic status. Also, women who are abused are at higher risk for acquiring STI's, including HIV/AIDS.[183]

Surprisingly, there were significantly more women in the PTL group who were either married or living with their partners (52.3% and 38.4%, respectively; p = 0.03) and according to the literature, single status is one of the risk factors associated with PTL.[80,81] Of the LR women, 63.6% were still living with their parents or other family, compared to 44.6% of the PTL group (p = 0.04). Women who still live with their parents may in a way be protected from some of the risk factors associated with PTL, such as unhealthy behaviour or experiencing violence, placing them at higher risk for infections and stress.

In terms of education, there was no statistical difference between the two groups. Alarming is the high incidence of unemployment among the women in our study population, which did not include maternity leave. Those women who have a high school education did not all finish matric (Grade 12), which may make it more difficult for them to find employment. The added burden of having to provide for a baby may place a woman at risk of being abused because of higher levels of stress.[190]

A very high number of women in both groups admitted to smoking cigarettes, 56.2% and 55.5% respectively. However, the women in the PTL group smoke significantly more cigarettes per day (p = 0.0019). Also, when the abruptio's and women with prior PTD were taken out of the PTL-group, the difference remained significant (p = 0.026). The finding of our study is not fully in agreement with others in terms of incidence – Campbell *et al.* found that only 17.7% of women who delivered preterm smoked.[241] However, McFarlane *et al.* found the incidence of smoking to be 49.5% among black and 59.6% among white abused women[233] and Stewart *et al.* reported that 72.2% of abused women regularly smoked cigarettes.[226]

Smoking during pregnancy has been associated more with abruptio placentae and LBW than PTL[250], but in this cohort of women we did not find that the 23

women with abruptio smoked more than the rest of the PTL-group or the LR-group. The number of abruptio's was, however, rather small. The high incidence of smoking in the PTL group may be a warning sign that these women are more likely to experience high levels of stress, which may include abuse. In addition, abused women may be less concerned about their babies and therefore not cut down on the number of cigarettes during pregnancy.

The most important and shocking finding of this study was the fact that 43.3% of women in the PTL group used alcohol, compared to 12.1% in the LR group [$p < 0.001$; OR 5.32 (2.53 – 11.4)]. Unfortunately, the measurement of the quantity consumed may not have been accurate as the sizes of beer bottles and glasses differ and a standard measurement was not given. The women were only asked how many glasses of beer they drank per weekend or per day. Women in the PTL-group may also have been more willing to disclose alcohol use, having just experienced a preterm birth and wanting to express any feelings of guilt. There are authors who have found the effect of alcohol on pregnancy outcome to be protective of IUGR and PTL.[264,267] Others have found that only heavy drinking is associated with IUGR and/or PTL.[265,266] More studies are probably needed in order to reach a more universal conclusion on the effects of alcohol on PTL, LBW and IUGR, but that will only be reached once a standardised measurement to determine the quantity of alcohol consumption is used.

Alcohol use is very common among women who are victims of violence and the fact that significantly more women in the PTL-group experienced physical or psychological violence at some point during their lives, may be an explanation as to why more women used alcohol.[233,250]

We did not find violence to specifically be associated with PTD, but those women who experienced violence were significantly more likely to engage in high-risk behaviour, which is "normal" for such a cohort of women. These women were not screened for bacterial vaginosis early in pregnancy, which is unfortunate, as

early colonisation of the genital tract with the associated bacteria, may also result from such behaviour and lead to preterm birth. Recent violence or violence during pregnancy did not significantly contribute to PTL in this study, although there was a trend towards significance, and the prevalence of abuse was alarmingly high (31.7% during the past year and 21.5% during pregnancy). The prevalence of violence during pregnancy in our community appears to be much higher than the numbers reported from other studies; for example, USA: 3.9 – 8.3%, Canada: 5.7 – 6.6%, Sweden: 11% and Nicaragua 13%. [225,227,228,184] A possible explanation is that the PTL group was specifically selected and thus not representative of the community as a whole. This group was also found to live an extremely unhealthy lifestyle, but whether that was as a result of violence suffered or the other way around, remains to e determined.

The community served by Tygerberg Hospital is mainly of low socioeconomic status. Although domestic violence does occur in all social classes, it seems to be more prevalent and more recognizable among the lower socioeconomic classes. Also, female empowerment, and in particular education, has been found to be protective against abuse.[190] The women in this study had very little education but it did, however, not differ significantly between the two groups.

Results from other studies on the effect of violence on PTL have not been consistent. [232] The most consistent finding has been the effect of violence on LBW[238], which is probably the result of stress, which, in turn, leads to smoking, poor weight gain, late entry into antenatal care and alcohol use.

Prolonged maternal stress, which is often the case in a violent relationship, may result in chronic elevated levels of CRH, creating an allostatic load. Such frequent stress, whether remembered or feared, will imprint itself upon a woman's HPA-axis prior to conception and may potentially alter the hormonal interaction between the mother fetus and placenta.[97]

These factors are all involved in a complex of potential pathways leading to preterm initiation of labour, almost always resulting in preterm birth. The multifactorial etiology of PTL is almost as complex as the multiple adverse effects that violence can directly or indirectly have on pregnancy outcome.

4.6 CONCLUSION

Domestic violence alone is not a risk factor for preterm delivery, nor will it ever be, because domestic violence does not occur as a single entity. Stress, fear, anxiety, depression or PTSD accompany domestic violence in most cases.[243,244,245] These psychological effects that physical, sexual or emotional violence can have, are often the reason why abused women will start to drink or smoke.[226,233,246]

Smoking is not only deleterious towards the fetus during pregnancy, but also during infancy and childhood. Children of parents who smoke are at greater risk for otitis media, asthma, bronchitis and pneumonia.[291] Preterm children may be at even greater risk. In addition, alcohol use by a women who delivers preterm may place her baby at higher risk for brain injury.[268]

Physical, sexual and psychological violence will, as long as it is tolerated in communities, continue in families as a vicious cycle. Children who are neglected may end up on the streets where they are easy prey for older boys and men to lure them into a life of sex, drugs and alcohol. These factors automatically place such children, especially girls, at risk for physical abuse. According to Kilpatrick *et al.*, substance abuse significantly increases the risk for assault. In turn, assault leads to alcohol and substance abuse, which increase the risk of further assault.[246]

Children who witness their mothers being abused grow up perceiving violence as normal and will likely do the same when confronted with similar situations. Girls may grow up to believe that women are inferior to men and has to submit to a man's every command. They also learn that men are allowed to punish them for "disobedience" and they learn to live in fear of men. These factors may cause a girl to be so eager to please a boy that she will do anything for him, including having sex when she does not really want to. Once she has had sex with him, he may think of her as his possession, starting the cycle all over again.
These cycles are extremely difficult to break. In order to do so the mindset of an entire population will have to be changed for any real effect. Educating men and women is therefore one of the most important strategies, but unfortunately parents and teachers are even today not willing to talk openly about relationships, sex and the dangers of substance use. "Experienced" peers thus teach many children on these matters and to fit in they do the same, even when they do not really want to.

Incorporating routine questions on domestic violence into antenatal care will only be effective with the appropriate training of midwives, doctors and nurses and will require a very good and safe referral system in order to be effective. Such practices will, unfortunately, take time, effort and the support of the government. Until such programmes can be implemented, educational talks, pamphlets and posters in antenatal waiting rooms may be a starting point. When a woman has symptoms that are associated with abuse, she should be confronted in a gentle, empathetic manner and if she discloses abuse, should be referred to a social worker.

Intervention in order to reduce maternal smoking and/or drinking has been found to be successful. Emons *et al*. found that motivational intervention (consisting of a 30 – 45 minute motivational interviewing session and four follow-up telephone counselling calls) among smoking parents or caregivers to children younger than three, reduced the levels of cigarette consumption by 10.1% and 7.5% stopped

smoking.[291] Such interviews and follow-up counselling may be helpful in reducing smoking among pregnant women. Once again, in theory it sounds good, but do we have the resources or extra staff that are equipped to do the interviews and counselling?

Chang *et al.*[292] reported that brief intervention on alcohol use during pregnancy at 16 weeks gestation had a positive effect of alcohol consumption among women who drank at that time. The intervention was structured as follows:

- Review the woman's general health and course of pregnancy to date.
- Review her lifestyle changes made since pregnancy, including smoking and alcohol consumption.
- Request her to identify her drinking goals while pregnant and her reasons.
- Have her identify circumstances when she would be tempted to drink.
- Brainstorm with her to identify alternatives to drinking when she is tempted.
- Summarise the session by emphasising key points and noting them in a manual ("How to Prevent Alcohol Related Problems"), which she could take home.

Women were asked to return postpartum for a follow-up interview and it was found that significantly more women were abstaining and those who were not, drank significantly less.[292]

Although there are no easy answers to solving the problem of ongoing abuse, providing information of referral agencies and literature will be helpful to women who are abuse survivors. Guiding abuse victims through pregnancy and childbirth, with knowledge and empathy, will also help them take another step toward regaining self-respect, power and trust. This will begin to break the cycle of abuse, one survivour at a time.

APPENDIX 1

DATASHEET

INFORMATION ON PREGNANCY

1. Date of delivery -----/----/-----

2. Age at delivery ----------

3. Gravidity: Parity: Miscarriage: Ectopic ---:---:---:---

4. Gestational age at booking ----------

5. Previous obstetric history (preterm labour, IUD, neonatal death [< 28 days], infant death [< 1 year])

Year	Gestation	Mode of delivery	Outcome	Complications

6. Last normal period ----------

7. Sonar (date; gestation) ----------

8. Medication during pregnancy (not for suppression)

a. Indication ----------

b. Type ----------

c. Dosage ----------

d. Duration ----------to--------

--

9. Chronic illness ----------

(None=0, Hpt=1, DM=2, Anemea=3, Heart=4, Psychiatric=5, TB=6, Other=7)*

10. Number of antenatal admissions (total): ----------

11. Antenatal admissions						
a. Days						
b. Indication						
c. Gestation						

12. Number of admissions for preterm labour ----------

13. Medication during admission ----------

14. Pregnancy complications ----------

(None=0, PE=1, Hpt=2, DM=3, Anemea=4, APH=5, SROM=6, Other=7)*

15. Number of antenatal visits ----------

16. Laboratory results:

a. VDRL ----------

b. Blood group ----------

c. Cytology (Normal = 0, ASCUS = 1, SIN = 2) ----------

d. Pathogens ----------

(*G. vaginalis* = 1, *T. vaginalis* = 2, *C. albicans* = 3, HPV = 4, non-specific bacterial infection = 5)*

e. U-MSU ----------

(normal = 0, contamination = 1, infection = 2)

DELIVERY

17. Date -----/-----/-----

18. Gestation ----------

19. Delivery: spontaneous = 1, elective = 2 ----------

a. If elective: ----------

(N.a.= 0, Termination = 1, Induction = 2, Caesarean section = 3)

b. Indication ----------

20. Mode of delivery ----------

(NVD = 1, Breech = 2, Forceps = 3, Vacuum extraction = 4, C/S = 5)*

a. Indication ----------

21. Maternal complications (postpartum) ----------

(None = 0, Infection = 1, Other = 2)

NEONATAL OUTCOME

22. Birthweight ----------

23. Apgar (1, 5, 10 minutes) -----:-----:-----

24. SGA* (Yes = 1, No = 2) ---------

25. Outcome ---------
(Normal = 1, Miscarriage = 2, IUD = 3, ENND = 4, LNND = 5, Infant death = 6)*

a. Final cause ----------

b. Primary cause ----------

26. Neonatal ICU (Yes = 1, No = 2) ----------

a. Days ----------

b. Indication ----------

27. Neonatal complications ----------
(None = 0, HMD = 1, NEC = 2, Sepsis = 3, NNJ = 4, Other = 5)*

28. Total days in hospital ----------

29. Discharged to secondary/primary institution (Yes = 1, No = 2) ----------

QUESTIONNAIRE

General

1. Marital status ----------

- Married = 1
- Single = 2
- Living with partner = 3
- Divorced = 4
- New marriage = 5
- Widow = 6

2. Housing ----------

- House owner = 1
- Rents house = 2
- Rent room = 3
- "Wendy house" = 4
- Room in house = 5
- Informal settlement = 6

3. Number of people living in house ----------

a. Adults ----------

b. Children under 16 ----------

4. Education ----------

- None =1
- Primary school = 2
- High school (any) = 3
- Tertiary education = 4

5. Occupation ----------

- None = 0
- Scholar/student =1

- Domestic worker = 2
- Factory worker = 3
- Hard labour = 4
- Professional = 5

6. Are you higher educated or earn more than your partner?
(Yes =1, No =2) ----------

7. Family income per month ----------

- < R575.00 =1
- R575.01 – R1 054.99 = 2
- R1 055.00 – R1 994.99 = 3
- R1 995.00 – R4 399.99 = 4
- > R4 400 = 5

Lifestyle

8. Smoking (Yes = 1, No = 2) ----------

a. Number per day ----------

b. Age when started smoking ----------

c. Passive smoker (Yes = 1, No = 2) ----------

d. Number of smokers living in your house ----------

9. Alcohol use (Yes = 1, No = 2) ----------

a. Type of alcohol ----------

- Beer =1
- Wine (red and white) = 2
- Spirits ("hard liquor") = 3

b. Quantity ----------

Weekends only

- 1-2 glasses = 1
- 3-5 glasses = 2

- >5 glasses = 3

Every day

- 1-2 glasses = 4
- 3-5 glasses = 5
- >5 glasses = 6

c. Does your partner use alcohol? (Yes = 1, No = 2) ----------

d. Does he abuse you when he drank? ----------

- Physical =1
- Sexual = 2
- Both = 3

10. Drug use ----------

- No = 0
- Marijuana =1
- Mandrax = 2
- Cocaine = 3
- Heroin = 4
- Other = 5

11. Does your partner use drugs? ----------

- No = 0
- Marijuana =1
- Mandrax = 2
- Cocaine = 3
- Heroin = 4
- Other = 5

Abbreviations:

*Hpt = hypertension

*DM = diabetes mellitus

*TB = tuberculosis

*PE = pre-eclampsia

*APH = antepartum haemorrhage

*SROM = spontaneous rupture of the membranes

*HPV = human papilloma virus

*NVD = normal vertex delivery

*C/S = caesarean section

*SGA = small-for-gestational age

*IUD = intra-uterine death

*ENND = early neonatal death (< 7 days)

*LNND = late neonatal death (< 28 days)

*HMD = hialine membrane disease

*NEC = nectrotising enterocolitis

*NNJ = neonatal jaundice

APPENDIX 2

ABUSE ASSESSMENT SCREEN

Example:

(Circle YES or NO for each question)

1. **Have you ever been physically or emotionally abused by your partner or someone close to you?**

   YES NO

2. **Within the last year, have you been hit, slapped, kicked or otherwise physically hurt by someone?**

   YES NO

   If yes, by whom (circle all that apply)

   Husband Ex-husband Boyfriend Stranger Other Multiple

   Total number of times_____

3. **Since you've been pregnant, have you been hit, slapped, kicked or otherwise physically hurt by someone?**

   YES NO

   If yes, by whom (circle all that apply)

   Husband Ex-husband Boyfriend Stranger Other Multiple

   Total number of times_____

Score each incident according to the following scale:

1 = Threats of abuse, including use of a weapon

2 = Slapping, pushing; no injuries and/or lasting pain

3 = Pushing, kicking, bruises, cuts, and/or continuing pain

4 = Beaten up, severe contusions, burn, broken bones

5 = Head, internal, and/or permanent injury

6 = use of weapon, wound from weapon

(If any of the descriptions for the higher number apply, use the higher number)

4. Within the last year, has anyone forced you to have sexual activities?

YES NO

If yes, by whom (circle all that apply)

Husband Ex-husband Boyfriend Stranger Other Multiple

Total number of times_____

5. Are you afraid of your partner or anyone you listed above?

YES NO

6. Why do you think men abuse women?

_____

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